Academic Collaboration with Contract Research Organisations: Reaching Out to the Right Expertise at the Right Time

While often considered to be the role of the pharmaceutical industry, drug discovery in academia is not a new concept.

The development of penicillin is an excellent example of how academia bridged the gap between basic biology and industry know-how. It was discovered in 1928 by Sir Alexander Fleming, when working at St Mary's Hospital in London, and in 1929, Fleming published his research results, noting that his discovery might have therapeutic value if it could be produced in a larger quantity. Fleming attempted to garner interest from the pharmaceutical industry to produce penicillin, but was initially unsuccessful. It was only at the onset of the Second World War that clinical trials with penicillin were performed and mass production ensued.

In the past 15 years there has been a growing trend by universities to spin-out biotech companies and to develop in-house drug discovery capabilities. An academic group or early spin-off company will encounter many challenges on its path of bringing a compound from the laboratory to clinical development. As is well-documented, drug discovery and development is a lengthy, complex, and costly process, entrenched with a high degree of uncertainty that a drug will actually succeed in reaching patients. Indeed, it has been estimated that it now costs around $2.6 billion to develop a new drug, and on average it can take up to 12 years to enter the market.

Seeking advice from the right experts at the right time, be it from a contract research organisation (CRO) or subject matter experts, is critical to a timely and successful drug development, and can alleviate costly mistakes that may lead to the failure of developing a drug that could bring a cure to thousands of people.

Once a drug has passed the initial discovery and invention stage, there are a number of key main stages in drug development where collaborative expertise can be necessary:

- Defining the drug's target product profile
- Formulation development and analytical work
- Non-clinical development
- Clinical development
- Regulatory review

Target Product Profile (TPP)

The first step is to set up a drug's TPP, which is a strategic document, highlighting the product properties that need defining from the outset. These properties will describe the minimal and ideal profile of a product such as its primary indication; the target patient population; what the dose form and dosing regimen will be; and what the desired efficacy and safety profiles of the product are. It is essential that these properties are well described, as they will form the basis of what the development design strategy will be going forward. A good understanding of the required properties will help design an effective and efficient programme of work.

Formulation Development and Analytical Work

Both small molecule active pharmaceutical ingredients (APIs) and large molecule biologics must be formulated to become medicinal products to be administered to patients. Pre-formulation work is a key step in the drug development process, and its main objective is to maximise the drug's efficacy and reduce potential side-effects. Various dosage forms exist, including oral solid tablets, softgels, pre-filled syringes, lyophilised powders, as well as topical creams and ointments. In each case, the choice of the final formulation will follow extensive stability studies and will have to meet the TPP criteria.

Analytical methods must be developed to monitor the critical quality attributes of the medicinal product. When used during stability trails or for batch release, they must be validated following appropriate guidelines.

Non-clinical Safety Assessment

There are several non-clinical safety studies that will need to be performed as part of the drug design, development and therapy process to move into first-in-human clinical trials. These include, although are not limited to, pharmacology, toxicology, safety pharmacology and genetic toxicology.

These will vary with therapeutic indication and the chosen route of administration. It is important to note that the drug design, development and therapy process will differ for small molecules and biologics.

Clinical Development

Clinical development starts with a well-designed first in human (FIH) trial. When planning a FIH trial, a carefully tailored design is mandatory to ensure safety and allow for further decision-making.

The design of this FIH trial should not be based only on the minimum regulatory requirements, or "good habits", but on bespoke scientific rationale. Depending on the pharmacological and safety profile of the drug, broader non-clinical data may be needed than those required by regulators to ensure not only safety, but also to increase the potential success of the development. Most FIH trials are randomised, double-blind and placebo controlled, but many other protocol aspects need to be decided, based on pre-clinical data only, such as:

- Should the compound be tested in healthy volunteers or patients?
- How many dose groups and subjects are needed?
- Will these be run sequentially, or in cross-over?
- What is a safe starting dose and dose escalation scheme?
- Besides safety, what else is important from a pharmacokinetic (PK) and pharmacodynamic (PD) point of view?

The FIH trial will form the basis of further clinical development and is a key milestone on the road to market.

Regulatory Interactions

Working closely with regulators is a key strategy for successful

drug development, and should not be seen as a barrier to be sidestepped or overcome. Building regulatory advice into a trial programme is an effective strategy to mitigate the regulatory risk inherent in product development, and to improve the likelihood of early product approval.

Requesting scientific advice from the correct regulatory body at the appropriate time has become an essential tool to guide product development, and can provide answers to many aspects of the development programme, such as:

- Has the correct and most appropriate animal model been chosen? And if there is no pre-defined animal model, is the proposal appropriate?
- Is the manufacturing process well defined and appropriate?
- Is the investigational medicinal product (IMP) well classified?
- Has the appropriate comparator for the patient studies been selected? Should it be a placebo or another treatment?
- Are there financial incentives for small and medium-sized enterprises (SMEs) to seek scientific advice from the European Medicines Agency (EMA)? How will it work with the US Food and Drug Administration (FDA)?

The frequency of the engagement, and the extent to which the regulators will be involved, varies significantly from compound to compound.

Much of the advice being offered by the FDA, EMA, and national agencies, is focused on helping companies, particularly SMEs, to prepare their medicines properly for clinical trials, by validating their non-clinical and early clinical strategy. However, quality aspects and the manufacturing process also warrant discussion early in the development process.

This is particularly true for a rising number of leading-edge innovations categorised as advanced therapy medicinal products (ATMPs), made from tissues, genes, or cells, which may offer ground-breaking new treatment opportunities for many conditions.

Conclusion

Drug development is a lengthy and winding road with many obstacles and challenges to be overcome. Nevertheless, with careful planning and consultation with experts at the appropriate stages of a drug's progression, it becomes an achievable journey.

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