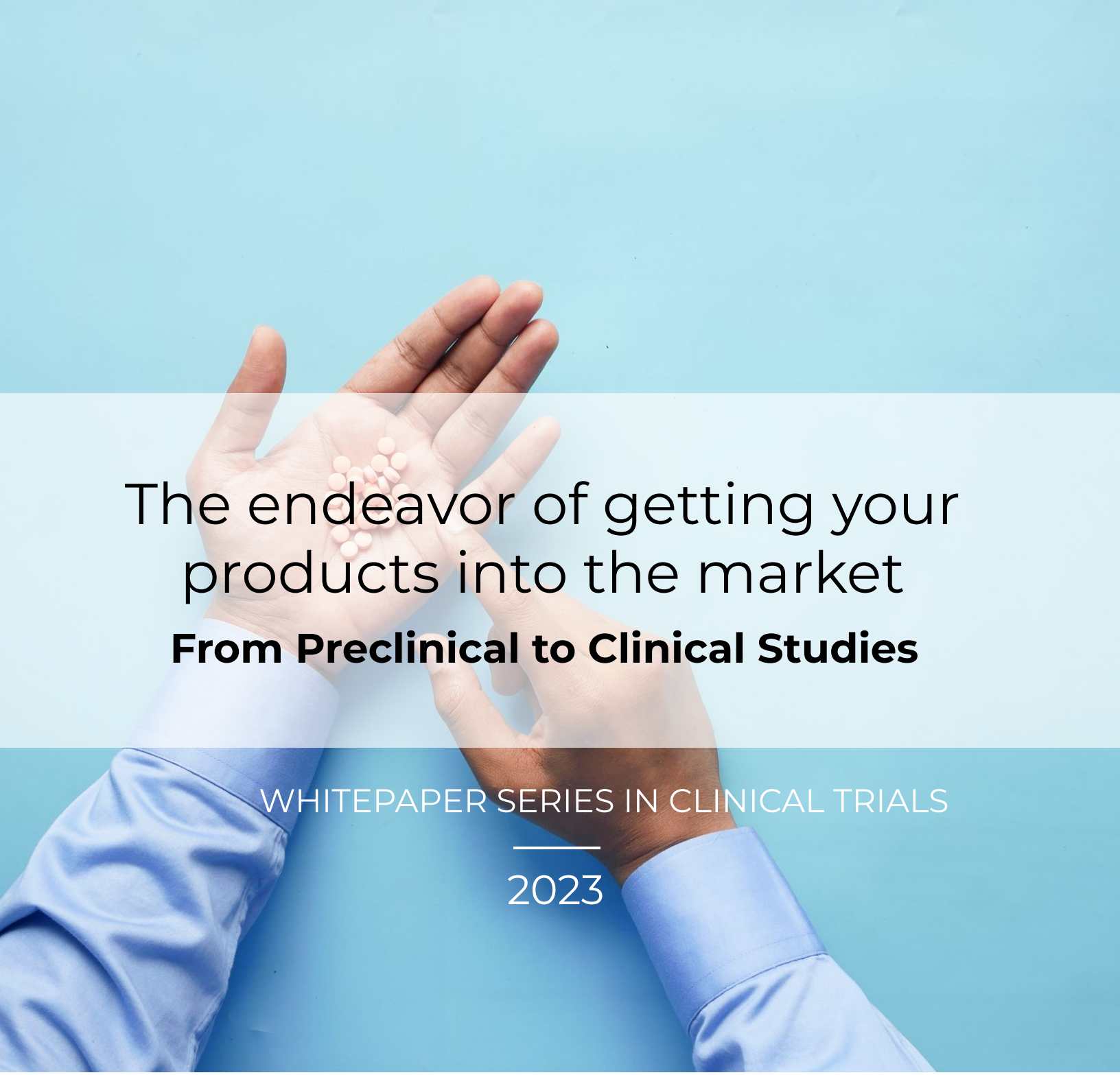

The endeavor of getting your products into the market

From Preclinical to Clinical Studies

WHITEPAPER SERIES IN CLINICAL TRIALS

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vector

drug development from bench 2 bedside

CONTENTS

For a smooth transition from preclinical to clinical research, the implementation of an efficient and strategic approach that can streamline your product development process is essential(8)

The endeavor of getting your products into the market

From Preclinical to Clinical Studies

The entire process from drug discovery through to preclinical studies and clinical trials in humans involves a long and challenging journey. The process can be financially risky and sometimes unpredictable(1).

Clinical trials in humans are highly regulated and are becoming increasingly complex. Therefore, in-depth knowledge of project management methods, the drug development process, and applicable regulations, is critical when defining successful strategies for the clinical development of a medicinal product looking towards obtaining marketing approval.

Navigating the sea of regulatory requirements and guidelines for acquiring market approval for a molecule can be a daunting task and start-up pharma companies may resort to hiring experienced companies for regulatory and project management support.

At **VectorB2B – Drug Development**, we have dedicated teams to help you transition from preclinical to clinical, offering 360-degree services along the R&D value chain.

Preclinical Studies

When deciding to move from bench to bedside, it is crucial to test if the drug under investigation (investigational product - (IP) is ready to be used in humans. Performing risk-benefit asses-

-sments is necessary prior to commencing early phase clinical trials (2).

Pre-clinical studies adhering to applicable regulations and guidelines should be carried out as part of the risk-benefit assessment:

- Preclinical safety studies (pharmacokinetics and toxicology) inform about the risks associated to the new molecule (i.e., the drug is not carcinogenic, mutagenic and/or teratogenic).
- Preclinical efficacy studies (pharmacodynamics) inform about the potential benefits associated with the molecule (the so called "clinical promise").

Extensive preclinical studies using animal models should demonstrate a favorable balance between safety and the clinical benefit/promise (efficacy). The type of preclinical studies undertaken is specific to the type of IP under analysis. However, certain studies, such as toxicology studies, must be always performed, regardless of the drug class in which the IP falls under. Toxicology studies are designed to identify any potential toxicities in humans who are exposed to the IP. The extent of these studies varies, depending on IP indication and type of molecule but, generally, a basic battery of toxicology tests is applied to all drugs to assess for adverse effects, when administered to one or more animal models, as a single dose or as multiple doses. The information collected during the pre-clinical stage of drug development is important for the design of Phase I clinical studies in humans(3). Preclinical studies allow for determining the initial dose of IP to be used in the clinical setting and help establish the safety evaluation criteria to be implemented during early phase human studies, including identification of the signs and symptoms that need to be monitored closely.

Multiple animal species should be used to gather basic information on the safety and efficacy of the IP that is being studied. In general, both the European Medicine Agency (EMA) and the Food and Drug Administration (FDA) require the use of good laboratory practices (GLP) for preclinical studies performed for IPs that are looking to reach the market. Exhaustive information about GLP can be found on the websites of the OCDE(4) and the European Commission(5), and on the 21 CFR Part 58.1: Good Laboratory Practice for Non Clinical Laboratory Studies(6).

The use of GLP-certified laboratories ensures the integrity, validity, reliability, and quality of non-clinical safety data submitted to competent authorities, as part of regulatory packages required for the approval of clinical studies and entry into the market.

When planning the preclinical program of a novel IP, several issues need to be considered. These include the definition of the target population, target disease-specific issues, the mechanism of action of the IP under evaluation, the adequate design of toxicology studies, the choice of suitable animal models that are representative of what occurs in humans (usually rodent and nonrodent mammalian models), the identification of the IP dose levels, the choice of the most suitable preclinical tests, among other factors(7).

At **VectorB2B** we have a Toxicology Team that can help you design suitable studies, with appropriate animal models to be used during your preclinical drug development program.

Furthermore, regulatory issues need to be properly evaluated.

Although regulatory agencies provide extensive guidance on the design and best-approach to develop appropriate preclinical safety studies, guidance on preclinical efficacy studies is limited(2). Besides, there are many preclinical studies that may not be required for the IP under evaluation. Therefore, the decision on what type of preclinical studies to perform is crucial. This decision will help Sponsors avoid undergoing unnecessary preclinical tests, that have a direct costly impact on their project budget and may jeopardize its success.

Transitioning from Preclinical to Clinical studies

For a smooth transition from preclinical to clinical research, the implementation of an efficient and strategic approach that can streamline your product development process is essential(8).

Another consideration to have in mind relates to the quality of the documentation and presentation of the preclinical results, which should meet the requirements of the Investigational and Medicinal Product Dossier (IMPD)(9) or the Investigational New Drug (IND) applications(10).

The aim of an IND is to obtain approval from the FDA to perform clinical trials of an IP in humans in the US. In Europe, the main document for EU Clinical Trial Application (CTA) is the IMPD.

IMPD/IND applications require detailed information on, but not limited to:

- Preclinical studies conducted previously to the application
- Manufacturing information regarding the IP
- Study plans and Study reports
- Investigator's Brochure (IB)

Manufacturing information aims to demonstrate that production and supply of consistent batches of IP can be achieved. Information pertaining to the manufacturer, composition, product stability and controls used for manufacturing the drug substance under evaluation must be provided(10).

At **VectorB2B**, the Chemistry, Manufacturing and Controls (CMC)/Process Development Team is dedicated to optimal process development and Good Manufacturing Practices (GMP) - or non-GMP - manufacturing, tailored to your product.

Writing an IMPD or an IND is a complex and time-consuming task that requires skillful and experienced people with relevant professional background and, preferably, medical writing experience. Understanding the regulatory requirements and the ability to interpret scientific preclinical and clinical data, identify incongruences and missing information, are key competences for success.

Strategically, when deciding which regulatory authority to apply to for market approval, the type of molecule and the target indication are factors of key importance. Different target indications demand application of the investigational product in different populations, which may be found in different countries. Thus, different sets of legislations may need to be followed for compliance with local regulations and compliance with the competent authority(ies) through which market authorization for the novel IP is being sought. Commonly, pharma companies apply for marketing authorization to the FDA and the EU via the IND and IMPD/CTA routes, respectively. However, other markets such as, for example, the Japanese, Chinese and Canadian markets may represent at-

-tractive alternative solutions. Understanding the main differences between the IND and IMPD regulatory processes and deciding whether the application should proceed via one or the other is key for the successful submission of your study(11) and future market authorization.

There is much information available from both FDA(12) and EMA(13) on how to conduct preclinical studies. However, having a dedicated team that complies with all the regulatory requirements and helps a Sponsor decide which preclinical tests are necessary to the development of its IP whilst ensuring accurate writing of IMPD dossiers, CTAs or INDs, is key for a smoother transition from preclinical to clinical research.

The **Toxicology** and **Contract Research Organization (CRO)** Teams can advise you on which preclinical studies are necessary to comply with the regulatory requirements to move into clinical setting.

Clinical Investigation

While preclinical research involves the study of drug safety and its effectiveness in animal models, clinical investigation refers to studies, or trials, done in humans(14).

Clinical trials involve various key stakeholders (Figure 1). A clinical trial is led by one or more principal investigators, mostly medical doctors. Clinical trials are sponsored by pharmaceutical companies, biotechnology companies, or others, and can be conducted in a single location (unicenter) or in many locations (multicenter).

FIGURE 1: Key players in Clinical Investigation according to the FDA(6)

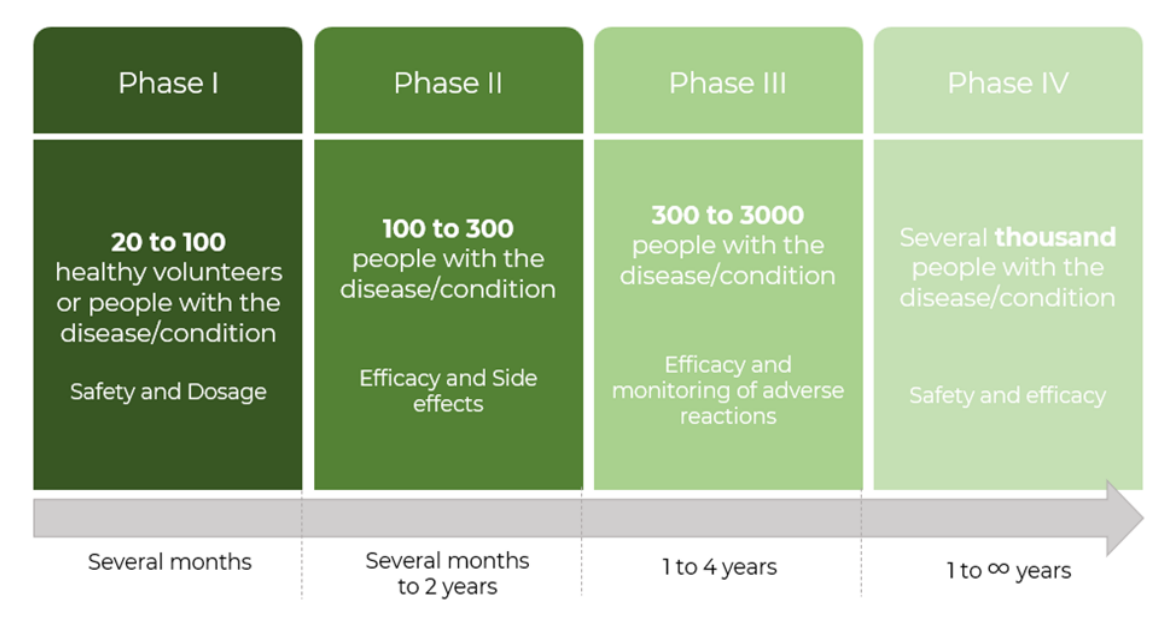

FIGURE 2: Phases of Clinical Trials(14)

Clinical trials must be carefully designed and developed prior to being approved by one or more regulatory agencies and ethics committees. These studies follow a specific protocol, carefully written and thoroughly revised. Clinical trials are conventionally classified in phases (Figure 2).

Although clinical trials are traditionally categorized into four phases (phase I through to phase IV), adaptive designs have often been considered to assess for futility, i.e., inability to achieve its objectives, and patient safety early on in the clinical development of an IP and improve efficiency and flexibility, whilst taking into consideration the ethics of minimizing patients' risks of exposure to ineffective treatments(15).

Clinical trials can also be classified as early phase clinical trials and late phase clinical trials, as overlap between phases may exist. Recently, Phase 0 studies have also been employed (use of small IP doses, microdosing or subtherapeutic dosing, in a reduced number of people) to test if a drug behaves as expected (e.g., the IP reaches its target) and provide hints regarding efficacy in humans(16).

VectorB2B – Drug Development focuses mainly on the early phases of the drug development process (Phase I+II) and on Phase III clinical trials.

For the purpose of this whitepaper, we will address these phases.

Phase I

Phase I trials refer to the first tests of the IP in humans (e.g., first-in-human, Single Ascending Dose and Multiple Ascending Dose studies). These studies usually involve a small number of healthy volunteers (20 to 80). In some areas, such as oncology, Phase I studies normally directly apply to patients with the target disease/condition intended to be treated by the intervention(17).

The main aim is to evaluate the safety and tolerability of volunteers to the drug. Therefore, Phase I studies are monitored closely, to collect information regarding how the drug interacts with the human body and how the body affects the drug (PK and ADME studies). The dosing scheme can be adjusted and is based on the results obtained in preclinical studies, as mentioned above. Treatment's safety, the safety dosage range, and side effects are evaluated. Approximately 70% of drugs move on to Phase II studies(18).

Phase II

Phase II studies are performed on larger groups or subjects with the disease/condition for which the drug is being investigated. The most common aim of phase II studies is to assess the efficacy of the drug and to continue the evaluation of the Phase I safety data. Information obtained from Phase II studies is important to establish therapeutic doses for the design of Phase III studies.

Phase II studies may include multiple studies of different stages(15):

- Phase IIa: Proof of concept (POC) study usually conducted with a small number of patients to demonstrate clinical efficacy.
- Phase IIb: Dose finding (DF) study which is usually conducted when Phase IIa demonstrates clinical efficacy. A DF study is performed to assess the efficacy as well as safety in a larger number of patients to find the optimal dose for Phase III trials.

To find the right balance between cost effectiveness and the number of doses tested during phase II DF trials is challenging. Testing a reduced number of doses limits the acquisition of knowledge regarding the IP, increasing the probability of selecting a dose that is not at the optimal therapeutic level. This approach may jeopardize further development of the IP during the phase III stage(15).

Thus, it is desirable to seek efficient approaches to correctly identify optimal dose(s) for phase III trials.
Approximately 33% of the drugs move on to Phase III studies(18).

Phase III

Phase III studies usually involve between 300 to 3,000 subjects who have the disease/condition for which the drug is being investigated. The primary purpose of phase III studies is to assess how effective the drug is when compared to existing drugs for the same condition (standard of care). This phase is usually called the "pre-marketing phase".
Phase III studies are multicenter and, when compared to the previous phases, longer, more expensive, and difficult to design and run. Rare and long-term side effects are more likely to be identified during this phase. In case the data obtained demonstrates that the drug is, at least, as safe, and effective as existing treatment options, the drug is usually approved by the regulatory agencies (e.g., FDA and/or EMA).

The challenges facing modern clinical trials

Modern clinical trials are complex and re-quire a complete understanding of the clinical research process. That is why Sponsor companies hire CROs as independent contractors with specialized knowledge to lead clinical trials and provide, for example, regulatory and project management services support in clinical research(19).

Sponsors and CROs need to form a close partnership, where expertise from both sides is shared and integrated, in order to achieve the defined objectives. Communication, flexibility and setting up clear expectations between both parties are critical ingredients for the success of any clinical development project. This is particularly important for small and medium biotech and pharmaceutical companies that are looking for fast results. Thus, CROs must adjust to its specific clients features by providing customized services that can answer to the individual needs of each sponsor.
Outsourcing individual services such as data management, pharmacovigilance, medical monitoring to expert providers, can represent vital strategies to respond to a Sponsor's needs. This approach allows CROs to become more flexible and respond to the requirements of a specific

clinical development project with tailored solutions, thus relying less on the traditional full-service model and its associated costs(20).

VectorB2B is a company that adopted the flexibility-response model. We have a team of dedicated and qualified staff that will fully support your project from drug discovery through to clinical trials implementation.

Clinical trial protocols need to be adjusted to the realities of different study sites, whilst responding to the requirements of the Sponsor, regulatory agencies and faster drug development programs with overlapping study phases and adaptive strategies. Protocol amendments must be approved before being implemented and comply with regulatory requirements. This can make a project more costly and time-consuming. Having access to data whenever needed, to address agile-data driven decisions, implies that trial processes and technology need to be optimized and work in parallel. Platforms for appropriate communication, audit trails and traceability must be assured. These are a few examples of the challen-

-ges for study sites and study managers that shape the modern clinical trial landscape(21).

In conclusion, each clinical trial is unique and must be customized according to its own operational challenges and objectives. Modern CROs need to adjust to the overwhelming complexity involving clinical research and face the specific needs of their clients.

VectorB2B – Drug Development focuses primarily on the needs of smaller biotech and pharmaceutical companies and offers tailor-made and flexible solutions throughout the clinical development process.

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VectorB2B offers the complete toolbox of basic and translational research in vision sciences, including animal models for a variety of diseases and in vitro techniques to test drug candidates and provide insight into the molecular and cellular mechanisms underlying the pathology.

Our specialists have a broad experience in the establishment of *in vitro* & *in vivo* experimental models and possess a wide range of technical skills to evaluate treatments for optic neuropathies

CONTACT


info@vectorb2b.com


https://vectorb2b.com/


VectorB2B - Drug Development

VectorB2B provides highly qualified services of drug discovery and development from the bench to bedside (B2B). It gathers the scattered capacities of the academic and industrial shareholders in the sector of health biotechnology to provide integrated services in drug discovery and screening, project design and implementation, pre-clinical and clinical scientific management, process development, and contract manufacturing (GMP). The shareholders are a strong and complementary set of academic partners and biopharmaceutical companies renowned in the health sector in Portugal. Together, they form a robust asset of knowledge and innovation, particularly in the domain of biological therapeutics.

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