

Beyond Financial Analysis – Scientific Due Diligence in Pharma and Biotech

Why is scientific due diligence essential in drug development?

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Introduction

"Due diligence" is a process of acquiring objective and reliable information, prior to a specific event or decision. It is a measure of prudence, activity, or assiduity, and ordinarily exercised by a reasonable and prudent person under the particular circumstances. In other words, due diligence means "making sure you get what you think you are paying for". Due diligence is not measured by any absolute standard but depends on the relative facts of the special case. In order to effectively perform due diligence, it is essential to have the understanding of what really matters with respect to the decision at hand. This requires expertise in various areas such as competitive pharma/biotech landscapes, the customer market place, operations, business development, strategy, business analysis, and last, but not least, technical or scientific expertise. Without this kind of experience and understanding, it is difficult to truly know what may be significant risks, specific to any given situation. Only this expertise guarantees that the significant risks are identified and quantified, that the right questions are addressed to the right people. Working according to a standard list will not suffice.

Although the financial history of a company is very important, a proper due diligence exercise goes far beyond the financial analysis. In science-based enterprises and projects, informed decision making is essential. This means scientific due diligence must be performed. Scientific due diligence includes a critical review of the development plan, a critical and independent assessment of the underlying scientific rationale and the achieved results, an analysis of the state of the art in the respective area, a comparison to developments of competitors, and last but not least, an evaluation of intellectual property, including patenting position and possible infringements. Sadly, scientific due diligence must also address the authenticity of any and all data since scientific fraud is, although rare, certainly a risk.

In summary, a well-conducted scientific due diligence process drastically decreases the chance of a wrong investment.

General Aspects

The ABC of due diligence

When it comes to due diligence, both parties are usually friendly and reveal everything that is requested, but one should have in mind that, usually, the parties may not volunteer information. That is why one should follow these basic rules:

A - Accept Nothing:

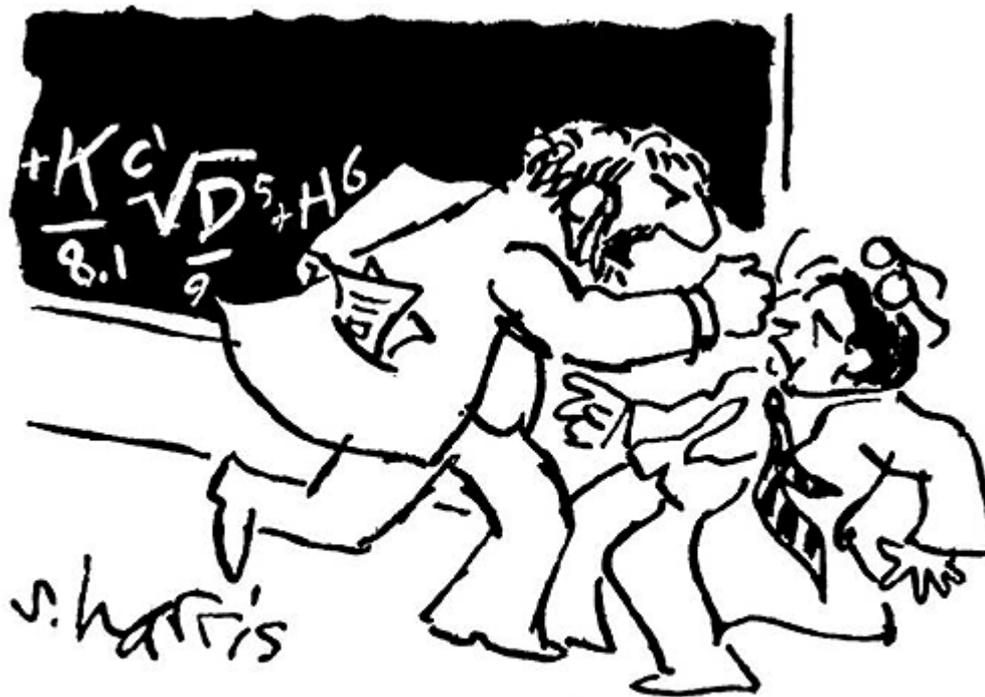
It is fundamental that all statements and facts must be checked and corroborated, regardless of their source. Many companies that undergo a due diligence investigation try to make friends with the persons involved in the due diligence process. They treat them like raw eggs, please them, and try to read their thoughts and wishes from their eyes, often with the hope of potentially influencing the results of the investigation. In this pleasant atmosphere, it is easy to directly communicate with the staff of the investigated company. An official get-together e.g. at a business lunch or dinner is usually appreciated by both parties as it gives the opportunity to learn more about the other party, including interpretations and information between the lines. However, it is of utmost importance that the reviewers remain unbiased during the period of investigation, which is why invitations to private or semi-private dinners, parties, etc. are usually accepted only after the due diligence process has been completed.

B - Believe No-one

In general, people who have been directly involved in the business or development process of a company under investigation are biased. They often become myopic or even blind to potential problems in their respective field. They, in general, tell you the truth, but always remember it is their truth, with their subjective colour. Even the most qualified people have opinions, sometimes strongly defended, but these do not necessarily represent the truth, even if presented as such. Over the years, often frictions between departments and even people have developed and it is hard to define who is who in this game. This makes it impossible during the process of due diligence to rely on verbal communication between the parties. Again, all statements must be verified independently.

C - Check Everything

Based on the above, it is mandatory to check every detail, to leave no stone unturned. The proper preparation of an individual check list prior to the start of your investigation is essential, and it is of the highest importance that this list is updated during the investigation whenever new information reveals the need for verification. In the due diligence process the same rules should apply as in the process of drug approval: "What is not documented does not exist!"



“You want proof? I’ll give you proof!”

Scientific Due Diligence

In the cases of Pharma and biotech, the areas of specific due diligence interest range from manufacturing through preclinical to clinical, regulatory and even marketing issues. Depending on the stage of development, due diligence may become more and more complex because all areas become interwoven e.g. regulatory is influencing all tasks, pharmacokinetics influences toxicology, both together have an impact on the clinical trials, and all together may direct the marketing strategy.

Regulatory

Drug Development is a highly regulated area. Many international and regional guidelines have to be followed and regulatory and scientific goals may not always be identical. Despite all recent efforts and achievements with respect to harmonisation of regulatory requirements, in particular by the International Conference of Harmonisation (ICH), there are still areas where results may be interpreted differently between Europe and the USA.

One of the most important questions is the definition of whether the drug to be registered is an **NCE** (New Chemical Entity), a generic, or even a hybrid. The answer to this question will have enormous impact on what is mandatory for a licensing application.

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Focussing on NCEs, some considerations are provided on what should be reviewed from a regulatory point of view. Special attention is paid to compounds that are in late stage preclinical or clinical development and which have not yet been approved.

First of all, a complete list of reports generated thus far should be asked for. This list should be checked for consistency and completeness. Checklists may be of help to conduct a systematic due diligence. Some generic checklists are commercially available, but they need to be customized, depending on the stage of development and of the compound to be reviewed.

While checking the development plan it should be challenged from a regulatory point of view e.g. is the proposed strategy for the compound in question realistic or not? Will the proposed endpoints be acceptable to regulatory authorities? Are there precedents to support this contention? The most important question is whether the envisaged indication is approvable, even if the proposed clinical trials have positive outcomes. For instance, some regulatory agencies in the **EU** may not consider 4th - or 5th-line chemotherapy of solid tumours *per se* to be reasonable indications. Whether the indication claim is too narrow or too broad should also be challenged. Here, input from marketing and clinical research is necessary and feedback from regulatory agencies and/or regulatory/clinical advisors (see above) is essential. Similar products which have been recently approved may be analysed, e.g. by reviewing relevant literature, European Public Assessment Reports (**EPAR**) in Europe or the Summary Basis of Approval (**SBA**) in the USA.

It is of utmost importance to check that all relevant pharmaceutical, preclinical and clinical guidelines, in particular those from the USA and the EU, have been considered and if not, why not and is the justification for not following the guidelines reasonable. Future guidelines and/or regulatory developments and guidelines should be anticipated.

A very important consideration is to verify that all available data to be used in regulatory dossiers fulfil compliance with certain principles in drug development, including **GMP** (Good Manufacturing Practice); **GLP** (Good Laboratory Practice), and **GCP** (Good Clinical Practice). Whether the audited company has established a system of quality assurance enabling these standards to be maintained should be checked. For instance, lists of available **SOPs** (Standard Operating Procedures) should be requested. The audited company should have performed self-inspections. Audits by regulatory agencies have already been addressed above. If contractors are used to conduct studies, the relevant contracts with these vendors should be reviewed carefully in order to confirm that the standards mentioned above are adhered to.

Applications which have been submitted to regulatory bodies to obtain permission to conduct clinical trials such as an **IND** (Investigational New Drug dossier) in the USA, a **CTX** (Clinical Trial Exemption documentation) in the UK and, from May 2004, on an **IMPD** (Investigational Medicinal Product documentations) in the EU) and the related correspondence with the agencies should be carefully reviewed. Summary documents (e.g. Investigator Brochures) should be thoroughly assessed.

Most likely, interactions with regulatory agencies will have taken place and they may have already been asked to comment on certain aspects of the development program.

Depending on the stage of development, there may have been pre-IND meetings, end-of-phase I meetings, end-of-phase II meetings, or even pre-submission meetings with the FDA. Also, so-called **Scientific Advice Meetings** with the **EMA** and/or national European agencies may have taken place. The audited party should provide the minutes of such meetings and all correspondence with the agencies. One task of the due diligence process is to ensure that the advice given by, and the agreements made with, the agencies have been followed. If there are deviations, this has to be investigated. In the EU, meetings with the national agencies may help to identify at an early stage of clinical development who may be interested in becoming Reference Member State (**RMS**) or rapporteur in the EU registration procedures (see below). This may have an impact in deciding where to place clinical studies.

During the development phase, there may already have been inspections by the agencies. Occasionally they inspect manufacturing facilities of finished drugs or active ingredients to ensure that these plants comply with the principles of GMP (Good Manufacturing Practice). Alternatively, they have inspected clinical sites or the facilities of a sponsor with respect to compliance with GCP (Good Clinical Practice). Reports on these inspections and relevant follow-up correspondence should be requested.

If the drug is manufactured abroad, any difficulties concerning importation should be examined. For instance, if the drug is produced in the USA and is intended to be exported to the EU, the European inspectors may ask to conduct a GMP inspection at the US manufacturing site, as there is still no agreement regarding a mutual recognition of GMP inspections in place between these two regions.

Another area of interest may be the question of whether the compound would qualify for Orphan Drug designation. This may be of particular interest for smaller companies which often develop drugs for rare diseases, as there are a number of incentives, including exclusive data protection for a defined period of time, tax reductions, or waivers of fees. There are some procedural differences in this respect between the USA and the EU. In addition the definition of the orphan drug status varies slightly between the various regions of the world. The threshold values in Australia are 1/10,000, in Japan 4/10,000, in Europe 5/10,000, and in the USA 7.5/10,000 citizens. Also, in the EU it is more difficult to get Orphan Drug designation on subsets of diseases.

In the EU, an analysis of whether the **MRP** (Mutual Recognition Procedure) or the **CP** (Centralised Procedure) would be the optimal route of registration should be performed. Both procedures have their advantages and disadvantages. However, at present biotech products and, in the near future, anticancer drugs and anti-HIV drugs must use the CP only. If, for example, the CP is chosen, a uniform trademark in all EU member states is required. Conversely if the MRP is chosen, the same drug may be marketed by different companies in the different member states.

In the USA, it is of importance to identify whether the drug may qualify for certain regulatory procedures, for instance fast track procedure, rolling submission, priority review, or accelerated approval. These procedures may mean that less data may be required for submission, that the application can be filed on an ongoing basis, or that the review time may be reduced.

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The quality of regulatory reports should be carefully reviewed for completeness, accuracy and issues of formality, but also for a cross-check of scientific validity. The electronic availability of these reports should be elucidated, since regulatory submissions will have to be made electronically in the near future.

In summary the following questions shall be addressed:

- Is the drug and NCE/NBE, a generic, or a hybrid?
- Have the IMPDs (IND, CTX, etc.) including their updates been available for assessment?
- Does the last version of the investigator's brochure contain recent results?
- Is the desired indication approvable and is the development plan sound?
- Has the registration strategy and history of comparable products been assessed?
- Have the correspondence and meeting minutes with regulatory agencies been made available and has it been checked?
- Have the guidelines of the various geographical areas been followed and if not are the justifications for the exemption appropriate or at least reasonable?
- Does the drug qualify for an "Orphan Drug Designation", or for accelerated review?
- Which procedure has been chosen for MAA in Europe, the MRP or the CP?

Manufacturing

The **CMC** (Chemistry, Manufacturing, and Control) section covers all information on physical, chemical, and pharmaceutical properties of the compound and the formulation. It is essential that the drug which is used in patients is produced following the GMP (good manufacturing practice) guidelines and some validation data on synthesis and the formulation process should be available.

In the **DMF** (Drug Master File), information can be found on synthesis and scale up, the chemical structure, molecular formula and molecular weight as well as the identity of drug product batches. This information contains hints on intellectual property issues, trade secrets and on the cost of goods. It provides information on the purity profile, potential by-products and the stability of the compound. It further illustrates how difficult or easy the scale up process is and how much time and effort is necessary to obtain sufficient amount of drug substance for phase III trials or marketing.

The auditor should assess whether the production process is validated and robust. Critical production parameters should be identified and appropriate in-process controls be introduced.

The general principles outlined in the respective **ICH** (International Conference on Harmonisation) guidelines (e.g. stability of active substance and drug product, stability, analytical procedures) and in the pharmacopoeias (in particular **USP** (United States Pharmacopoeia) and **EP** (European Pharmacopoeia).) should be observed. Differences between the 2 pharmacopoeias should be described. Specifications, analytical results and testing methods should be evaluated for regulatory acceptance. In case of parenteral products, sterility and pyrogenicity should be evaluated.

Special attention may be paid to batch consistency. The impurity profiles of the different batches used in preclinical and clinical studies have to be compared. Scale-up procedures, changes in the production equipment or the manufacturing site or the formulation during clinical development should be thoroughly monitored. If the active substance is known to be critical from a bioequivalence point of view, a bioequivalence study comparing the batch produced according to the old procedure with that produced according to the new procedure may be necessary.

- Is the Drug Master File of the active substance available? If so, can the Open Part of this document be provided?
- What is the reputation and reliability of the manufacturer of the active ingredient and the finished product? Is GMP fulfilled (see above)?
- Are the analytical methods appropriate and are they sufficiently validated?
- Have appropriate reference samples been used?
- Are the basic requirements with respect to presentation forms (e.g. tablets) and analytical methods compliant with the respective pharmacopoeia?
- Is the active substance associated with properties known to cause regulatory questions (e.g. chirality, stereoisomerism, isomorphism, hygroscopy, low solubility, poor stability, light and/or temperature sensitivity), and have they been appropriately addressed?
- Have impurities been identified and toxicologically qualified?
- Are the excipients which are included in the formulation of the drug toxicologically known? If unknown excipients are used, they have to be included in the preclinical testing strategy.

Preclinical

The description of **Primary Pharmacology** shall provide detailed information on *in vitro* and *in vivo* activity and on how the drug works. It also should elucidate the mode of action of a drug substance in relation to its desired therapeutic target. The objective of **Secondary Pharmacology** is to reveal the mode of action respectively of effects which are not target related, whereas **Safety Pharmacology** is to determine potential undesirable pharmacodynamic effects on physiological functions.

The **Pharmacokinetics** in animals will give first clues on **ADME** (Absorption Distribution Metabolism Excretion/Elimination) in general and more specifically on Half-life, Dose linearity, and Drug-drug interaction and thus provide safety information for the first study in man.

The basis for all pharmacokinetic and toxicokinetic evaluations are validated bio-analytical methods. For classical small molecules physicochemical methods (**HPLC** [High Performance Liquid Chromatography], **LC-MS/MS** [Liquid Chromatography - Mass Spectrometry], **CE** [Capillary Electrophoresis] etc.) are in general sufficient. For biologics often a bundle of different methods (immunological assays, bioassays, etc.) is necessary to establish the compound properties regarding pharmacokinetics.

Whereas plasma concentrations of small molecules are often related with the pharmacodynamic effect and show “S” shaped response, this may not be valid for biologics where bell shaped curves are not the exception.

Thus, the evaluation of a **PK-PD** (Pharmacokinetic-Pharmacodynamic) relationship may be much more difficult to establish especially in the early development, but it is nevertheless essential for the choice of the appropriate clinical dose and schedule. Therefore, other technologies (e.g. immunologic assays, cell-based assays, bioassays) have to be used for biologics as the classic tools of physico-chemical analysis and ADME can hardly be used for humanized antibodies or other large molecules.

The assessment of **Non-Clinical Safety** studies should, with reference to the development phase, check the completeness of the program, the quality of the studies and their documentation, and the choice of the animal models which should be justified and, if necessary, re-challenged during clinical development. The following questions should be addressed as far as possible:

- What are the possible routes of administration and are they suitable for the intended indication, disease severity and patient population (amount of absorption by different routes, oral availability, food influence)?
- Can the adequate exposure of the animals be granted in toxicokinetic studies, i.e. if the drug-substance was added to the food? Was the relationship between dose and exposure linear?
- What is the bio-distribution pattern of the drug in qualitative and quantitative terms (protein binding, tissue distribution, volume of distribution)?
- Does the compound have the chance to reach the target tissues in relevant amounts?
- What are the metabolic pathways (*in vitro* / *in vivo*; in man and in the species used in toxicity studies) and are they sufficiently similar to establish safety?
- Which enzymes or enzyme systems are involved and how likely are interactions with other compounds, nutrition and life style components.
- What is the circulation time in the body (half-life) and will it be adequate for the intended dosing frequency, duration of treatment?
- What are the elimination pathways (clearance) and what are the risks for necessary adjustments of the posology in patients with impaired function with respect to the safety margin?

The elementary goal of **Toxicology** studies is to understand the toxicity of the candidate drug well enough to make a judgment whether it is safe enough to initiate clinical trials. The toxicology profile of a new drug substance shall meet the clinicians' requests which are dependent on the intended indication and may be characterized by the following questions:

- Were the chosen animals relevant models for predicting human toxicity?

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This question is of special importance for testing of biotechnology products, where the therapeutic target may not be present in animal models and where immunogenicity has to be addressed.

- Was the used test material comparable to the product proposed for or used in the clinical trials?
- Was the route and frequency of administration adequate for the planned clinical trial?
- What dose/exposure produced toxic effects in animals?
- What dose/exposure did not produce toxic effects in animals (**NOAEL** [No Observed Adverse Effect Level])?
- Was the dose-effect relationship linear?
- What could be a safe starting dose in man?
- What were the signs and duration of toxic responses?
- Did effects differ following single and multiple dosing (accumulation of toxicity)?
- Were the toxic responses reversible? What were the target organs and systems, what is the dose limiting toxicity (DLT)?
- Was the toxicity expected for the chemical class? Are toxic metabolites produced?
- Was accommodation to the toxic effects observed?
- Does the duration of the performed toxicity studies support the clinical trials planned?
- Do the performed toxicity studies support the phase of clinical development and the treatment of the target patient population?

This is of special importance if women of childbearing potential are included.

As the human trials progress, the drug substance moves from non-clinical subchronic studies through chronic and developmental studies and oncogenic evaluations to support longer-term and broader efficacy studies. Attention should be paid to potential differences between the USA and the EU with respect to preclinical requirements despite the ICH guideline (e.g. duration of chronic toxicity studies [EU 6 months, US 9 -12 months], design of immunogenicity studies).

The pivotal non-clinical safety studies should be conducted following the guidelines of **GLP** (Good Laboratory Practice).

Ultimately the potential benefit of a **NCE** (New Chemical Entity) or **NBE** (New Biologic Entity) has to be weighed against the potential risk/toxicity. An often asked question is: "What toxicity profile would cause a company to stop the development of a new drug candidate?" There is no simple answer to this as this is mainly dependent on the severity of the disease to be treated. In other words, it is the ratio of risk to benefit which is decisive. A good guidance as to what might be an acceptable safety profile may be, if available, approved drugs of the same class.

Clinical

The protocols of all clinical studies, finished and ongoing, should be reviewed with regard to design, statistical power, and endpoints. Specific attention should be paid to the question of whether these studies are or were adequately designed to achieve the intended goal and whether the endpoints are appropriate.

All clinical trials should be conducted according to the guidelines of **GCP** (Good Clinical Practice). At least the most important trials, specifically those, directly influencing conclusions as to dose selection, efficacy and safety, and those designated as “pivotal” should be audited by an independent **QA** (Quality Assurance) unit. The respective documentation should be available during the due diligence process.

The documentation should contain the permission to conduct the studies (**IND / IMPD** [Investigational New Drug / Investigational Medicinal Product Dossier]) as well as the **Ethics and/or IRB** [Institutional Review Board] approval, all protocols of initiated studies including all amendments, and sample **CRFs** (case record form). End of study reports, or at least statistical analyses, should be available for all finished trials and, for ongoing trials, it is helpful to assess interim analyses, if available. At least the main results must be available to be evaluated. Often it is argued that the data of ongoing studies cannot be made available because the data are blinded. In this case at least contacts with the obligatory **DSMB** (drug safety monitoring board) and access to the enrolment data should be allowed. Without checking these data it is impossible to compare the clinical development plan with the actual data. In the case where the clinical development is still ongoing this crosscheck is the only way to estimate the time which is needed to complete the development.

As there may be country or continent specific differences in what is considered to be acceptable or even required for approval e.g. in Europe or the USA, it may become necessary to conduct continent specific trials. The differences may include the state of the art treatment of specific indications but also the selection of endpoints.

It is highly advisable that the comparator treatment, the endpoints and the required significance of the delta to the comparator treatment are discussed or, even better, agreed upon with regulatory agencies (**EMA/ FDA** [European Medicinal Products Evaluation Agency / Food and Drug Administration]) before they are initiated. These discussions should also impact the design of pivotal trials, e.g. blinded or open trials. Studies designed to be double blind may cause severe logistic problems but they are the only way to avoid any bias, even when “objective” endpoints are chosen.

Special attention should be paid to Adverse Events. All available information on this topic should be requested and analysed together with a clinical drug safety expert. It should be ensured that all reporting requirements have been fulfilled.

Oncology

In principle, clinical trials in oncology follow the same rules as studies in non-oncologic indications, but with some exceptions. The risk benefit assessment, for example, would accept more toxicity of a new compound than in the indication of hay fever. Another difference is the need to achieve approval for each sub-indication, i.e. first, second, third line therapy of breast cancer, colon cancer, etc. Experience has shown that a substance is not equally effective in all tumour indications. In addition, the indications with the highest incidence usually create a high competition of clinical studies between competitive companies.

An important question is whether there is a met or unmet medical need. If, for example, in one indication an established therapy achieves cures in the majority of patients, e.g. testicular cancer, it will be hard to demonstrate superiority of a new compound. On the other hand if the established therapy leads to unsatisfying results and the new compound shows superior efficacy and/or a more favourable safety profile, marketing approval is easier to achieve.

Anticancer therapy has always been an individual therapy and, for over a decade, progress in therapy has been due to the selection of the right therapy for a given patient or for a given patient population. Real breakthrough therapies like the introduction of cyclophosphamide, doxorubicin, cisplatin, or taxanes have been rare.

Recently, with the introduction of molecular targets, the individual therapy approach has become more successful. Monoclonal antibodies against specific types of breast and colon cancer as well as for specific lymphoma achieved approval. However, these new, specific target oriented therapies required a paradigm-shift in the selection of endpoints, from demonstration of efficacy as monotherapy in pivotal trials to the possible combination of the new compound with established treatments as add-on-therapy.

In general, the most important factor for success is the speed to market, followed by speed to peak sales. Having this in mind it might be a successful strategy to select the most promising indication of a compound and focus on pivotal studies in this indication, even if it is a niche indication. Niche indications may be honoured by the agencies by granting an orphan drug status, which usually is combined with an expedited review, with reduced registration costs, and even with extended exclusivity periods.

All of the following questions should be answered with yes.

- Were all protocols, CRFs, and results of all finished and ongoing clinical trials available?
- Were the studies adequately designed to achieve the intended goal?
- Have they been performed according GCP and have they been audited? Has the IRB approval for the studies been documented?
- Was there enough time to review IND/IMPd documentation including their updates?

- Were there contacts with the agencies (FDA/EMA) available and were they recorded?

For oncology products it is of special interest to assess the following questions:

- Has the indication been identified which may facilitate the fastest way to approval?
- Is it beneficial to get an orphan indication status?
- Which is the indication for peak sales, and how and when can approval be achieved in this indication?

Phase I

The most important goal of phase I studies is the assessment of the drug's **safety profile**. By determination of the **DLT (dose limiting toxicities)** the specific organ toxicities in man are evaluated. In oncology, it is important to define the **MTD (maximum tolerated dose)** which in general serves as the recommended dose for phase II trials. This holds true mainly for cytotoxic agents, where usually an exponential dose-response curve is seen. In non-oncology indications and for biological agents in oncology, a safe dose range, encompassing an assumed **minimal effective dose (MED)** should be established in order to determine “**the optimal**” dose. If at least biological activity has been observed the therapeutic window can be assessed.

During phase I, **pharmacokinetic studies**, complementary to the safety evaluation, will elucidate potential differences between human and animal tissue distribution, absorption, metabolism, excretion pathways, half-life, dose linearity, drug-drug interaction, and the influence of dose and schedule.

- Are appropriate bio-analytical assays available?
- Is the dose plasma/blood concentration linear? (What would be the issues or consequences if not?)
- Was the compound tested in the target population?
- What is the extent of intra- and inter-patient variability of blood or serum levels?
- Were the **ADME** (Absorption Distribution Metabolism Elimination) parameters in preclinical testing adequate and predictive for studies in patients?
- Have studies in patients with diabetes, renal, or liver insufficiencies been performed? Are the pharmacokinetics different?
- In case of oral administration - is there a food interaction?
- Is there a potential drug-drug interaction?
- Were differences detected between genders and between children, adults and elderly?
- Which questions e.g. regarding special populations, comedication etc. still need to be answered for a full application dossier?

The results of these studies will have a great impact on the selection of dose and schedule as well as the route of administration in further phase II and III clinical trials.

Depending on the mode of action and the availability of respective surrogate parameters, first hints as to efficacy may be expected. Thus phase I trials may already give an answer to the question whether **clinical proof of concept** has been achieved yet.

As a prerequisite for continuation of the clinical development at least biological activity should have been observed.

Phase II

The goal of clinical phase II studies is the assessment of the drug's **efficacy**. In principle, there are two ways to look at efficacy. The first step may be the proof of concept demonstrating biological activity which is followed by the clinical proof as a second step. The definition of efficacy depends strongly on the chosen indication and varies widely.

In cardiology, for example, the normalization of blood pressure or cholesterol may be regarded as first signs of efficacy. However, the ultimate goal is reduction in the incidence of myocardial infarction, or insults, and ultimately prolongation of disease free survival. This is similar in oncology where tumour shrinkage, stabilisation of tumour growth or prolongation of time to progression are considered to be first signs of efficacy. Also here, the ultimate goal is cure or prolongation of survival. In other cases however, where patients are symptomatic, palliation of the disease may be the ultimate goal of treatment.

If the endpoints of phase II studies are time to progression or prolongation of survival it is necessary to perform randomized phase II trials, as historical comparisons usually will not suffice.

Another important goal of phase II studies is the determination of the optimal dose and schedule and maybe even the optimal route of application.

Phase II trials usually also reveal practical issues, such as problems with the handling of the drug in routine hospital- or outpatient situations.

In oncology phase II studies in various tumour indications serve as screening to determine the most promising indications with regard to speed to market and speed to peak sales. This screening also helps to figure out whether the designation of an orphan drug status is possible or even desirable.

If an orphan drug designation is possible and the respective phase II results are favourable, this orphan indication may become the lead indication, as regulatory fees and assessment time may be reduced and market exclusivity for a certain period may be granted. The definitions and regulations vary slightly between US, EU, and Japan.

The results of the phase II trials with limited numbers of patients per study will usually create the hypothesis for the design of phase III studies, although in exceptional cases, a conditioned approval may be granted even with phase IIb data, especially if medical need is high and unmet, the indication is rare, the results are absolutely convincing, and derive from multicenter trials.

Phase II is the decisive part of the clinical development since, up to this point, relatively little money has to be spent because the number of patients is limited.

The most important questions of phase II are:

- Has efficacy been achieved and is the expectation concerning efficacy fulfilled?
- What is the definition of efficacy?
- Are there sufficient hints to hypothesise that the new compound is superior, either with respect to efficacy or safety?
- Can a phase IIb trial lead to approval?
- What would be the risks in a consecutive phase III trial and how many patients are needed to demonstrate significant superiority or non-inferiority?

Phase III

The ultimate goal is the definitive proof of clinical efficacy e.g. by showing cure, prolongation of survival or disease free survival, or at least palliation. The typical study design usually compares the new compound alone or in combination, with alternative / established therapies which are considered as **state of the art**. The “gold standard” design is the Randomised, Controlled Clinical Trial (**RCCT**), if necessary and feasible, double-blind. In order to obtain marketing approval it is the rule, that at least two confirmatory trials showing an adequate clinical benefit are requested by the authorities. However, if outstandingly positive and clinically meaningful results are achieved, an approval may be granted if only one confirmatory but absolutely convincing trial has been submitted.

The selection of primary and secondary endpoints as well as the selection of the comparator treatment is one of the most important factors that determine success of pivotal trials. The most accepted endpoints are **prolongation of (disease free) survival, prevention of life-threatening events** or **palliation**, if there is an unmet medical need. Another well accepted endpoint is **improved drug safety**, if superiority in this respect can be demonstrated. Surrogate endpoints may be accepted, especially in the case of rare diseases with high unmet medical need, or if the active ingredient is unchanged from an already-approved agent, i.e. liposome, nano-particle, or **PEG** (Poly Ethylene Glycol) formulations.

The selection of the comparator **state of the art treatment** may be dependent on the geographical area where the approval is sought. The FDA favours placebo-controlled studies, in contrast to the EMEA which prefers active control groups. In some cases it may be wise to select a non-approved treatment in a third arm, specifically when it may be expected that this new, not yet approved treatment may become the future state of the art therapy.

In other words, the anticipation of what may be the future state of the art therapy in a specific indication, shall impact the selection of comparative treatments in pivotal trials. (Note that non-approved treatment arms may necessitate collaboration with another company who may or may not be willing).

In addition to the type of analysis, i.e. test for non-inferiority or for superiority, the frequency and the time points of interim analyses should be discussed with the agencies. It is important to realise that the study design of the pivotal trials will have an impact on the labelling when and if the drug is approved. All these parameters are typically confirmed in meetings with regulatory agencies and, as details really matter, a review of the correspondence with the agencies and respective meeting minutes is mandatory for a proper evaluation.

The crucial questions at the end of phase III are:

- Are the selected endpoints appropriate and have they been achieved?
- Is the delta clinically significant / relevant / convincing?
- Are all regulatory requirements fulfilled and have the commitments previously agreed with the agencies been met?
- Are the results still in favour of the new compound or have other compounds with potentially improved safety or efficacy profiles appeared on the horizon meanwhile?

Marketing

Marketing should be involved in the development of new compound from early on. A series of facts, such as classification as NCE or “me too”, practicability, indication-specific competitive environment (who is a potential competitor at the expected approval time), access to market, and market potential/size will have significant impact on the marketing strategy.

Although at first glance appearing as minor issues, topics such as trademark, trade name, and **INN** (International Non-Proprietary Name) should be addressed. The registration of a global trademark may be a time-consuming and expensive process. In numerous cases a legally “clean” trademark has been objected to by the agencies for reasons of consumer protection. This should be clarified with the agencies very early on. As already mentioned, in the EU a trade name acceptable from a regulatory point of view in all Member States is very important, especially if the CP is intended for **MAA** (Marketing Approval Application). The **INN** is the scientific name of an active ingredient (for example acetylsalicylic acid, trademark Aspirin) which has to be applied for at the WHO in Geneva. The INN is required for an **NDA** (New Drug Application) in the USA) or the **MAA** in EU).

Other marketing aspects causing sensitivity with the regulatory field include co-marketing, in the EU separate marketing companies in different Member States, and pack sizes.

In addition, it should be clarified early on in the development process whether the envisaged indication is reimbursed by the health insurance systems.

In the USA, for instance, MEDICAID or MEDICARE may not pay for certain treatments (e.g. in the past, oral chemotherapy). In the EU, the social systems are not harmonized at all. The reimbursement policies vary from member state to member state.

There are numerous EU member states which require an “additional approval” based on pharmaco-economic data. Therefore, a pharmaco-economic strategy should be implemented in the development plan as early as possible. Often separate pharmaco-economic studies may be required for individual countries.

The following questions should be addressed:

- Is the drug reimbursable?
- Have pharmaco-economic studies been performed?
- Is the INN and the trademark “clean” and accepted by all respective regulatory agencies?
- Are there practicability issues?

Patent Research

Patent research will usually be out-sourced to specialized patent-law firms where patent coverage and expiry dates are checked, and investigations on countries in which patents are already granted respectively issued are performed. A “freedom to operate” opinion is often required even when a company has issued patents.

Regulatory data protection may be critical, especially if the patent protection is relatively short. Currently there are different regulatory activity periods in the EU. For the time being, some member states grant 6 years, others 10 years when the MRP is chosen whereas the CP provides 10 years in the entire EU. This will be harmonised in November 2005 when 10 years of data protection will be granted irrespective of the chosen registration procedure. One additional year of protection can then be obtained if a second indication is approved during this period. In the USA, usually 5 years of data exclusivity are granted for an NCE. This can be extended by another 3 years, if a new indication is approved within these 5 years. An additional 6 months may be gained if the drug is developed for a paediatric indication. In both the EU and the USA, the patent life can be extended by 10 or 7 years respectively, if an orphan drug status has been granted. The patent life can also be extended by a maximum of 5 years, both in the US and in EU, if a first approval is obtained within the period of the first patent protection. In the EU this is called **SPC** (Supplementary Patent Certificate). In the US, this extension comes under the Patent Term Restoration Act and is intended to compensate patent holders for the protracted period of development and the regulatory process.

Conclusions

After completion of the due diligence process the following key questions can be answered for a single project, the product portfolio, as well as for the entire R&D department:

- Is the rationale for the development scientifically sound, does it comply with the current regulations of the areas where marketing authorisation is applied for, and has proof-of-concept been reached?
- What are the strengths and weaknesses of the development plan and is it practical and effective?
- What are the strengths and weaknesses of the compound? Are the achieved results indicative of an improvement over what already exists or what will become available soon?
- Is the development truly innovative?
- Are there any “deal-breakers”?
- What is the market potential of the new compound? Will it be reimbursed?
- How strong is the patent coverage?
- How long is the protection period of the compound?

Authors:

After 15 years in the clinics and another 15 years in the pharmaceutical industry where he has been responsible for clinical development in three companies, Professor **Konrad Burk** founded ClinDescience GmbH (www.clindesc.com). ClinDescience cooperates very closely with experienced preclinical, clinical, and regulatory experts from Europe and the United States and offers its assistance and expert knowledge in clinical development to pharmaceutical and biotech companies, as well as scientific consultancy and due diligence service to venture capital firms.



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