Scientific due diligence

A handbook for investigators and investors

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Foreword

Licensing of intellectual property is common in the pharmaceutical world, many a blockbuster drug began as a simple agreement between a start-up and big pharma. Any company in the field will have a multitude of potential technologies which they *could* license for further use. The challenge, however, lies in finding the correct one.

This is where scientific due diligence comes in, the independent, realistic and critical review of the intellectual property. From early development data through to clinical study results, patents to competitor analysis, the due diligence process provides a strong basis for any investment decision. Yet due diligence is complex, requiring the combined efforts of a team of specialists. A quick and effective due diligence requires that the investigators know what they are looking for, regardless of their field of expertise.

To help those investigators, we have developed this handbook. It provides a guide to the most important parts of scientific due diligence, the approaches to take, the areas of particular concern. The advice contained here will help you to perform a thorough and successful due diligence of a biotech or pharmaceutical company.

The book has been divided into sections which cover the entire due diligence process.

The first section covers the basics of due diligence, the preliminary investigations, and the preparation required prior to the on-site visit:

- Chapter 1 introduces due diligence investigations, including the attributes of good due diligence investigators, the basic rules to follow, and commonly-seen licensing approaches.
- Chapter 2 covers the initial steps of assessment, including the preliminary screening for potential licenses and the secondary screen to identify true opportunities.
- Chapter 3 shows the preparation for the on-site scientific due diligence investigation, including typical organisational tasks and team set-up.

Next, the specific requirements for each area of expertise are covered in more depth:

- Chapter 4 covers the investigation from the regulatory affairs perspective, including factors such as approval risk, regulatory planning, and useful special pathways.
- Chapter 5 deals with quality, the assurance that the technology has been developed and manufactured to the required quality levels. The chapter covers typical GMP documents and important GxP requirements which will need to be verified.
- Chapter 6 covers chemistry, manufacturing and control, the details of the product and the production process. This includes manufacturing-site specific documents and the process development and validation requirements.
- Chapter 7 describes preclinical trials, the preliminary work prior to human testing. This includes approaches for evaluating preclinical studies as well as more specific information for toxicology and pharmacology work.
- Chapter 8 involves clinical trials, the most important test of any new drug. This section covers both general trial requirements as well as those specific to individual clinical phases.
- Chapter 9 deals with marketing, the ability to sell the new product. This includes determining market position, analysing potential competitors, and determining reimbursement options.

- Chapter 10 describes the intellectual property factors which may be involved, covering both patenting and data exclusivity approaches to IP protection.

The last chapter deals with the close-out of the investigation:

- Chapter 11 finishes the scientific due diligence process by providing the final set of questions to ask prior to making the final recommendation.

Finally the five appendices provide reference information which will help when conducting a due diligence investigation:

- Appendix I provides information for those on the other side of a due diligence investigation, with best practices and mistakes to avoid while being audited.
- Appendix II provides an example checklist of questions to cover during a due diligence investigation, split into the same categories as described in this text.
- Appendix III provides an example list of documents which should be requested during the investigation. This is ready to be customised according to your specific requirements.
- Appendix IV lists the currently available ICH guidelines for Quality, Safety and Efficacy. These underlie much of modern pharmaceutical development and so are a useful guide for the acceptability of a firms' development program.
- Appendix V lists specific terminology used in this document (these terms are highlighted in **bold**) as well as useful sources of information.

Introduction

Licensing of intellectual property is a common occurrence in the pharmaceutical world, occurring when the inventor of a new technology grants another company the right to use their invention. There are many reasons to follow a licensing route and most of them start from a lack of capacity – the inventor does not have the money, expertise, or facilities required to fully develop their invention. Instead they turn to larger companies, exchanging the right to develop and exploit the invention for an up-front payment or continuous royalties.

Biotech or pharma start-ups are typical users of licensing agreements. Very few small firms have the resources needed to run a clinical trial or development program themselves, thus many aim to develop their technology to a certain point and then license it out. Pharma companies are always looking amongst these options for new intellectual property to gain an edge over the competition.

Yet there are many thousands of newly patented ideas out there. How does a company know they are licensing the right thing? This is where the art and science of due diligence comes in.

Due diligence is one of those terms which is often thrown around in office conversations, but one which is rarely understood. Due diligence is a vital part of the investment process and it involves, at heart, making sure that what you are buying is what you think it is.

What does this mean? The most typical case occurs when a company is looking at buying another company, a piece of technology, or the rights to market some sort of product. There are lots of smiles, fancy brochures, and impressive looking PowerPoint slides – all of which seem to say that this purchase is the best idea in the history of corporate investments. Yet before your company gives away several million dollars, they want to be sure that there are no unpleasant surprises lurking behind the buzzwords and pie charts. This is where due diligence comes in.

The people performing due diligence need to find reliable information on the potential investment, only then can management decide whether the deal should go ahead. They need to sort out the facts from the hype, the commercial realities from the over-excited claims. It is a difficult job and one which requires that you be an expert in many areas – only then can you truly evaluate if the possible risks are actually problems.

Financial due diligence tends to get the most attention, but due diligence is not confined to the balance sheets alone. Just as important is the investigation into the science behind the investment – are you about to buy a potential blockbuster drug or a costly flop? Do you know all the potential side effects or the true mechanism of action? There is a lot of money in the world of biotechnology and pharmaceuticals, and it is up to scientists to help decide whether it is being spent correctly.

This is where the concept of *scientific* due diligence comes into play. It involves an independent, realistic and critical review of the underlying technology, the scientific rationale and results obtained so far, a comparison to the potential competition in the field, a check of patents and other intellectual property. And this is just for the most open and honest of potential deals – sadly a number of promising new ideas are only promising because of outright scientific fraud and forgery.

Scientific due diligence is vital for ensuring that investment money goes to the right place. As someone with a scientific background, you will often be involved in these checks – which means that you will need to understand what to look for.

Chapter 1. An introduction to technology licensing and due diligence

Due diligence is a thorough investigation of the available documents and data by a team of experts. The aim of this investigation is to predict the chances of success and the potential revenue which will come from any particular investment. Due diligence is performed by every group aiming to invest a large amount of money – from venture capital funds through to big pharma.

The investigation will be performed by a team of people with varying specialisations, each providing a different viewpoint into the chances of success. As a rough guide, the entire process will follow a series of steps as detailed here:

- Initial screening will identify potential partners for technology licensing or acquisition
- The preliminary team members will join up and assess publically available information, thus beginning the secondary screening step. This will be used to develop an initial idea of the technology's value.
- The potential partner is contacted and discussions regarding licensing begin.
- The full due diligence team assemble and confidentiality agreements are signed. Preparation for the on-site investigation begins. Information from internal sources and primary research (such as interviews with key opinion leaders) is gathered.
- The due diligence team performs their investigation of the partner's documentation, usually in person at the site. This will include expert assessments of regulatory, preclinical, clinical, sales, marketing, CMC, supply chain, and various other fields.
- The team will provide their assessment in a final report. This is then used by management for the final decision on investment.

Once the investigation has been completed there are several different options which may be taken. By far the most common is the decision not to go ahead with the investment, to walk away from the deal. The opposite option is to go ahead with the investment, assuming it delivers a reasonable return on investment and suits the firm's requirements. The third possibility involves the renegotiation of terms or payments prior to investment.

The ideal due diligence investigator

The first question many ask is – who should be involved in the due diligence? This depends on both expertise and talents. The good due diligence investigator should understand their field as an expert, but there are also several additional attributes which they need. They should be analytically minded, thorough, and accurate, with excellent attention to detail. The common phrase is that it is better to review too much than too little – the small items you ignore as irrelevant are usually those which turn into deal-killers later on. Investigators also need to have excellent communication skills, they will be working with a team and thus need to clearly broadcast their important discoveries without ambiguity.

Many companies will run a number of due diligence checks in a short period of time, which means that availability of experts can become a limiting factor. In general the more complex the deal, the greater the time, number and expertise of the experts required. As a rough rule of thumb, a small due diligence will require 1-2 weeks of preliminary background work, 2-3 days of onsite review, and a few weeks afterwards to bring everything together and determine the conclusions.

In general you should expect to be communicating all issues that arise *as* they arise – not a few days later or the next time you think about it. Although it's important to follow the planned investigation, it is equally as important to have the flexibility to chase after new bits of information. Most

investigation groups will also have a daily wrap-up or discussion to go over important topics, this may sometimes involve preparing written summaries as well. By the end of the investigation each expert will be expected to provide an opinion on the project's chance of success, including likely costs, timelines, and potential issues.

Basic rules in due diligence

All due diligence relies on a couple of basic rules, regardless of the technology being investigated or the field of expertise. They are as follows:

- Check everything
- If it wasn't documented, it wasn't done
- No-one tells the entire truth
- You are not there to make friends

This seems simple enough, but actually holding to these rules in the fast-paced atmosphere of the due diligence investigation is *much* more difficult. The following sections will cover this in more detail.

Check everything

Check everything. Everything. Not just things which seem important, not just things which have a major effect on the success of your investment, not just the things your manager wants you to focus on. Check everything. Because you never quite know when one thing will pop up after a completely innocuous question and change the entire scope of the deal.

This is harder said than done, of course. You will never have unlimited time to chase down every last detail, which means that you will need to prioritise the areas which represent the highest risk. Only when you are sure that the real deal-killers are out of the way will you turn to the little bits and pieces of information.

How do you keep track of this? Using checklists, usually. A checklist will contain an overview of all the potential problem areas which you and your company can think of. This allows you to systematically and comprehensively follow up on everything, secure in the knowledge that you won't forget something vital halfway through. This checklist will be updated as the investigation goes on and new information is brought to light, ensuring that it remains constantly relevant.

We'll cover the creation of a checklist and the typical items to be followed in the following sections.

Documents, not opinions

There is a phrase in the pharmaceutical industry which states that "if it wasn't documented, it wasn't done". This applies during development work, during regulatory filings, and most definitely during audits. It does not matter how convincing a tale your experts can spin, if they cannot show a documented piece of evidence supporting it then they will not be believed.

This phrase also applies in the world of scientific due diligence. Your job is to find out the facts of the matter. Facts, not opinions. If something has never been written down and documented, particularly in the world of biotech and pharmaceuticals, then it was probably never done. No matter what the group being investigated says.

No-one tells the entire truth

Everyone has their own biases, be they conscious or unconscious. Those who work for a company under investigation will want the investigation to reach a good outcome – they want the sale to go ahead, the licensing deal to be signed, they want that money in their bank account. Regardless of their level of personal honesty they will have some sort of stake in achieving success, and this leads them

to shade their responses to your questions. You may find that some aspects or risks are downplayed in conversations, others may evade potentially difficult topics or questions.

This gets even more complicated when office politics enters the picture. Different groups will have different ideas about who should get the credit and the blame, investigations may bring up long-buried difficulties, assumptions and downright errors that everyone has forgotten about. You may even find that one group does not actually want the purchase to go ahead – this may be due to fear of losing political power or even blatant malice towards those who will benefit. Sorting through this minefield of differing opinions can be maddeningly complicated. Yet it needs to be done.

In practice this means that you will need to verify every statement or communication. Remember that you cannot take any statement at face value. Even the most perfectly knowledgeable and honest of experts may accidentally say something wrong – and most people are neither perfectly knowledgeable nor perfectly honest.

They are not your friends

The investigators in a due diligence check have an amazingly powerful role, their final recommendation can sink a multi-million dollar deal if the right set of unacceptable risks are found. There is thus a vast amount of pressure on the firm being investigated to make the due diligence investigators happy. They will be helpful, cheerful, they will bring you coffee and muffins and invite you to dinner and drinks after the long day of trawling through dry documents.

Why do they do this? Because it works – it has been shown time and time again that a personal or emotional connection leads us to make non-rational decisions about others. Happy investigators are more likely to overlook or downplay risks, simply because they feel a connection to the employees of the other firm and so don't want them to be disappointed. This is a danger even for experienced investigators. It is thus vital to remind yourself that these people are *not your friends*.

This does not mean that you should be cold or aloof – friendly professionalism will help you to get the information you need far more effectively. Yet you should remain professional and unbiased for the duration of the investigation. Decline gifts and invitations while the investigation is in process, because even the most innocuous of things can subconsciously influence your decision-making process.

Types of licensing

The transfer of technology or intellectual property from one company to another is a common occurrence, one in which many different models of transfer or investment are possible. Most commonly, a large pharmaceutical firm will invest in a small start-up to gain access to their new and exciting technology. This model fuels much of the biotech start-up industry – university spin-off companies will develop a newly-invented technology to the point that it can be sold to big pharma, making their founders rich.

Alternatively a large firm may license one of their less-promising technologies to a smaller firm, one which may be better able to use it. This occurs because large companies have more potential leads than they know what to do with. There is enough money to take the most promising through to approval but many less-tempting options will be left by the wayside. By licensing these options out, the company will make a small amount of income from an otherwise abandoned project.

A further alternative involves two firms of equivalent size but differing focus working together to bring a product to market. The main difference between licensing and partnering is that both parties now have a strong stake in the success of the project, leading to greater efforts and buy-in from both sides.

The specifics of the licensing agreement are as flexible as the imaginations of the parties involved. Eventually, however, they will be specified in a legal agreement between the **licensor** (the

inventor/holder of the intellectual property) and the **licensee** (the company which will take over development/use of the invention). This legal agreement will include the details of what the licensee can do with the invention, how the licensor will be compensated, and what obligations or rights the two sides will have.

Compensation for the inventor is almost always financial, though the exact format varies from deal to deal. It may consist of an upfront payment (transferred directly on signing the licensing deal), milestone payments (paid when certain goals are reached, such as entering clinical trials), or royalties (a set amount or percentage for each unit sold once the product receives marketing approval). The amount provided in each component will be a matter of negotiation. Due to the inherent riskiness of new drugs, licensors will usually attempt to keep the majority of the compensation in the milestone or royalty categories so as to reduce their losses if the project fails.

There are several types of licensing which may be used, each with advantages and disadvantages which are described in the following sections. All of these options will require a due diligence process from both parties to ensure that the deal is as rewarding as hoped. From a due diligence point of view, the least complex form of deal is that of a marketing agreement or licensing agreement, followed by the more complex joint venture. The most complex deals, and thus the heaviest due diligence requirements, occur when an entire company or technology is being purchased. This provides the greatest level of risk and thus requires the greatest level of caution.

Exclusive licensing

The licensee can be granted an **exclusive license**, the right to be the sole user of the technology. In other words, the licensor cannot sell the rights to further companies, nor can they use the rights themselves. This is by far the most common licensing approach in the pharmaceutical world and is the *de facto* standard for small biotech companies.

Exclusive licensing can, however, be granted for certain subsets of the technology. Thus a company may grant an exclusive license to one company to use their patented technology in Europe, another company may have rights in the United States. Further approaches may grant licenses for different applications or medical indications. This is, naturally, a weaker form of 'exclusive' licensing and so is comparatively harder for small companies to obtain.

Partnering

There are several forms of partnership which may occur. Two companies may enter into a **joint venture**, in which a new, free-standing enterprise is set up and used to develop a product with pooled resources from the two companies. This is usually designed as a co-development agreement, in which they agree to share the risks, costs, and eventual profits of a piece of technology. Joint ventures normally have a fixed lifetime, after which they will dissolve or one party will buy out the other.

This approach is often used by companies of a similar size which have differing specialisations – a clinical study firm and a manufacturing company may enter into an alliance to pool their expertise and so bring a new drug to market. As the risks and potential profit are shared by both sides, the payment to the technology holder is correspondingly lower than a more one-sided transfer such as exclusive licensing. It does, however, allow the licensor to obtain a larger share of the eventual revenue.

Alternatively an alliance or corporate partnership involves a direct agreement between the two parent companies. It is most often seen between a large, well-capitalised pharma firm and a smaller company with very little money but a very good technology. The agreement usually includes an equity investment in which the larger company takes control of a certain percentage of the smaller.

Marketing agreements

Marketing agreements involve the granting of the right to sell a product or family of products. No intellectual property is transferred in this kind of arrangement, making it a relatively risk-free process for the technology owner. This approach is most often seen when two pharmaceutical companies have

well-developed marketing networks in different regions, say Asia and Latin America, and then work together to reach those markets. It is a more collaborative approach, in that the two companies will expect to share in the revenue developed from the granted regions.

Acquisition

Why obtain a license when you can simply buy the technology outright? The acquiring company takes control of the invention and can then make the decision to develop it or to license it to others. Purchasing the technology provides you with full ownership of the risks and rewards, yours to deal with as you want. This *disadvantage* of this approach is that most early-stage projects will fail, the risk of not getting a pharmaceutical out of an acquisition is very high. This means that payouts for early acquisitions are low (to account for the risk) and thus the profit for the seller is minimal. This combination of risk and low payment means that acquisition is less popular in the pharmaceutical world than the other models.

Chapter 2. Initial steps in due diligence

There are many options for licensing in the world, yet only a few are right for your company. How can you decide which ones are the best match? The most effective approach involves two rounds of screening prior to in-depth discussions and term agreements. These steps need to be performed quickly and cheaply, they aim to rapidly screen out unsuitable deals and thus avoid lengthy, time-consuming investigation.

First a preliminary screen will be performed to identify potential deals from the vast pool of technology on the market. Promising technologies will be further investigated in a secondary screening check. This uses openly-available information to determine if the next step, an in-depth due diligence investigation, should be taken.

The following sections will cover these two initial steps in further detail.

Preliminary screening

When your company is in the market for new technology, it is easy to be overwhelmed by the sheer number of potential licensing options. Many, many companies and research groups have technology to offer – very few of these offers are worth your time. It is therefore important to have a quick 'general' screening process, this allows the time-wasting options to be quickly discarded before evaluating the true potentials.

This initial screening process should take several factors into account, including portfolio fit, risk/benefit, and the nature of the licensor.

Portfolio fit

Possibly the most important question you can ask is 'does this technology fit with my current business?' Is the compound similar to others which your company has in the pipeline or on the market? And if yes, is this what you want to have?

Similar products means that the company already has experience in a therapeutic area. This tends to make a complementary technology easier to develop and you can leverage currently-existing manufacturing and marketing expertise. The disadvantage of a focused product portfolio is that new regulations or competition will affect all of your products – i.e. you may suddenly find all of your products are affected by an unexpected change. By contrast, a non-related technology may let you broaden your portfolio and thus the overall risk. However to do this you will need to hire or train more experts to deal with the new ideas and processes.

Portfolio fit also depends on the nature of the drug in question. The typical example here is biological drugs. Many companies have expertise in the development and marketing of small-molecule drugs, yet are comparatively clueless in the new and complex field of biological therapeutics. You should be sure that the nature of the drug (e.g. biologicals, gene-editing) are appropriate to the firms' current expertise and portfolio experience. Jumping into a new 'hot' field without preparation is a great way to lose a lot of money.

Risk/benefit

Is the technology worth it? Or, more appropriately, is the technology worth it to your company? Every company has a different level of risk tolerance – some may target risky new drugs while banking on exceptional profits if they manage to reach approval, others will prefer the lower-risk and lower-reward of follow-on products or generics. You should check whether the risks and benefits of the technology match your firm's internal risk tolerance. Although it is possible to move from a low-risk to a high-risk portfolio, this needs to be carefully managed to avoid internal strife and office politics.

Risk is a particularly important factor for pharmaceutical companies because the success rate for new drugs is ridiculously low. As a rule of thumb, a company which performs initial studies for one

thousand promising compounds will find one which is suitable for clinical testing. Of those which enter clinical studies, less than 10% will successfully progress to approval. Worse, reaching the market can take 12 years from the first development work and cost around a billion dollars. These numbers clearly show why risk tolerance (and the ability to absorb a failure) is such an important factor in any decision.

Interestingly, the chances of reaching approval differ between targeted indications, as seen in the following figure. This progression likelihood is often negatively correlated with expected returns. Oncology drugs, for example, are notoriously difficult to bring to market, but once approved can expect to make significant revenue.

The Licensor

In almost all cases the licensing of new technology will require a long-term business relationship between the inventor and the licensee company. Thus you also need to take the nature of the licensor into account when deciding if the technology is worth your time.

A very basic question to ask is 'why does this company want to license their technology?' There are many possible answers to this, but the most common reasons are company focus, portfolio fit, or capabilities.

The focus of a pharmaceutical firm will be relative to its size. A multinational pharmaceutical giant requires large amounts of revenue, such as that provided by a blockbuster drug. Thus a promising candidate for a small market may be useless to that company simply because the expected return is too small for their requirements. Rather than waste the resources required to develop this compound, the large company may instead license it to a smaller one. The smaller company has lower revenue requirements and is thus better able to target the smaller market.

Portfolio fit applies to the target indication as well as the expected revenue. A compound may be identified during development, but initial results show that it is suited for an indication which is outside the firm's normal field of expertise. Rather than broaden the portfolio, it may be preferable to license the technology out to another firm who are specialised in the new area.

Lastly, some companies may simply lack the capability to properly use the technology. The typical example here is a spin-off/start-up company developing a discovery from academic research. Lacking the cash to perform expensive pre-clinical or clinical trials, they need to find a larger partner to share costs and expertise. This is not limited to start-ups, some firms may specialise in pre-clinical development and use licensing to take the identified compounds through to approval.

The reason for licensing is important because it provides information on what the licensor thinks of the technology. If a company is definitely capable of developing a promising compound, yet decides not to, this may imply that it is not as promising as they are claiming. Always question the reasoning provided by the licensor – does it actually make sense given what you know of their capabilities? Are you getting slightly evasive answers to your questions? Both of these are warning signs and you should be very careful before progressing with the evaluation.

Identifying competitor products

We discuss the approach for identifying competitor products in a later section, but in general an initial check for potential competition should be performed during the primary screening phase. This will usually involve searches online, more targeted searching of the scientific literature, discussions with experts and key opinion leaders in the field, and sometimes hiring consultants in the field. This initial check should provide the company with an idea of whether they will be entering a crowded market or an empty one. This in turn will affect the decision to progress with the due diligence process.

Secondary screening

The primary screen removes the majority of unsuitable licensing options. The next step involves a slightly more detailed investigation, an initial run of information gathering prior to entering into 'serious' discussions with the company of interest.

This requires checking a number of different sources, then compiling the information together for a preliminary report, (no single document will contain all required information exists – and it would be heavily biased if it did). This preliminary report will be used to decide whether to proceed with discussion of licensing terms and in-depth due diligence. Even though the underlying information is compiled from public sources, you should consider the report to be confidential – it represents a significant source of 'business intelligence' for the company.

The information used for the report may be drawn from many different sources. Chief amongst these are:

- material from the company
- industry/scientific publications
- online sources
- industry reports and expert opinions
- regulatory guidance

Material from the company

Most companies with aims to license their technology will produce a large amount of material intended for the public or potential investors. This material will usually be freely available from the company website. It may include formal publications such as annual reports or more marketing-based work such as press releases, product introductions or investor guides. The majority of the documents will be written for non-experts or the public, thus providing an overview of the technology which is ideal for introducing yourself to the field.

More specific information will be available in scientific publications written by now-employees of the company. University spin-offs in particular will host copies of the original journal articles in which their discoveries were first described. Although the technology has (hopefully) developed further, these articles will provide an excellent view into the underlying science.

Industry and scientific publications

As mentioned in the preceding section, scientific publications from the company being investigated will provide an insight into the science behind the license. This will normally be specific to the technology, but will assume a certain level of familiarity with the field. More general searches of scientific journals will help understand the scientific basis of the area of research – for example, the pros and cons of a particular drug class or of recent competing discoveries in the field. Review articles are good for overviews but often lag behind the cutting edge of science – you will find better answers by checking 'real' publications and their associated editorials.

Moving on from the scientific journals, there are no end of websites, newsletters and magazines covering the pharmaceutical world. It is possible that some of these will have covered the company or technology of interest – these will provide further information and alternative points of view. While searching you will be hoping to find assessments or descriptions of the safety and efficacy of the target technology, this may come in the form of articles, press releases, interviews with key opinion leaders, etc. Many of these articles will compare and contrast similar or alternative technology, giving you a starting point for your competitor analysis.

Online searches

Practically everything can be found online these days, the data you can obtain is often limited only by your patience, time, and resistance to frustration. Time, however, is the limiting factor at this stage, so you must quickly focus on the most useful sources for information. We list a number of useful online resources in a later section which may help, however some of the first stops should include:

- The FDA website, in particular **Drugs@FDA** portal. This database provides a lot of information on drugs, excipients, approvals and warnings. It hosts copies of correspondence between the FDA and drug companies which will help identify FDA thinking on specific topics.
- The **Orange Book** (properly known as the *Approved Drug Products with Therapeutic Equivalence Evaluations*) provides information on drugs which have been approved by the FDA. This includes patent and exclusivity information, which allows you to identify timelines for generic competition. (https://www.accessdata.fda.gov/scripts/cder/ob/)
- **ToxNet** provides a wide range of information on the toxicological effects of many chemicals and drugs. It is an excellent first stop for checking potential toxicity effects for drug classes under investigation. (https://toxnet.nlm.nih.gov/)
- Scientific literature may be accessed via many different portals such as PubMed, Thomson Web of Science, or Google Scholar. Literature may provide information on efficacy or safety of the drug in question, it can also be used to determine data on potential competitors.
- Regulatory affairs information can be obtained from industry groups such as **RAPS** (the Regulatory Affairs Professionals Society), which publish regulatory news and updates on important topics. (https://www.raps.org)
- Clinical trial information can be obtained from **ClinicalTrials.gov**. This database lists almost all clinical trials currently active, completed or planned in the highly-regulated markets.

If all else fails simply spending a few days searching will usually turn up a lot of useful information, often hidden away in old publications or abstracts. Company representatives will often visit large conferences in their disease field, where they will present posters with summaries of their work. Although the posters themselves are usually discarded, the abstracts are commonly listed online and provide otherwise-unavailable information on internal studies.

Industry reports and expert opinions

The knowledge business is a vast one and there are many companies whose sole business is collating information to sell to others. Information brokers, consultants, or industry analysts – all can be contracted to provide research reports on the technology or the disease area being examined. This can be very expensive but can save a lot of time and money during the initial stages.

Alternatively, you can choose to interview experts or key opinion leaders in the field. With a deep background in the area of interest, these experts will often have insights that you may not otherwise be able to obtain. These experts will normally charge a fee for their time, often a very hefty one. It will, however, be cheaper than a complete research report from a consulting company.

Regulatory agency documents

Regulatory agencies such as the FDA and EMA publish a number of documents as part of their commitment to transparency. There are many different documents available and each provides a different level and type of information. Guidance documents provides an insight into regulatory thinking, approval and committee minutes document the marketing status of other competitors, inspection-related findings show whether potential manufacturers or clinical research organisations are competent and reliable.

The summary review, sometimes known as the summary basis of approval (SBA), is a document summarising the information evaluated during the drug approval process. This is *usually* freely available via the FDA database and can be used to identify the regulatory hurdles overcome by similar drugs of competitors. This in turn helps you to plan your eventual marketing approval strategy.

Chapter 3. Preparation for scientific due diligence

Once the screening process is complete, things will get serious. Discussions with the company over licensing conditions will begin, terms and counter-terms will be exchanged, and a date for the due diligence investigation will be set. It is very difficult to say just how long a due diligence investigation will last as it is heavily dependent on so many factors. Generally the fastest it could take is 1-2 weeks, usually only in cases where *both* sides put all possible resources, enthusiasm and commitment into the investigation. Alternatively you may have half-hearted investigations in which data is hidden and experts prioritise other work – these can take months or even years.

Planning ahead helps to avoid a long, tedious investigation. Indeed there are many things which will need to be done well before the due diligence can begin. Foremost amongst these is setting up the team, but there are many housekeeping and organisational tasks to finish as well. Once these are complete, the experts will be ready for the detailed investigation into the specific requirements of their respective fields.

Setting up the team

A new medication will progress through various stages of development, from initial idea through to filled-and-packaged drug. This process requires a complex mix of experts, each with their individual specialisations and roles. This complexity is mirrored in the process of scientific due diligence. No-one will have all the knowledge required for a full due diligence investigation, there is simply too much to learn. Instead the due diligence will require a team of investigators, each with their own specialisation and background.

The complexity of the investigation, (and thus the number of people involved), will increase as the project moves closer to market authorisation. At early stages, where the majority of the data has been generated in the laboratory, somewhere between 5-15 people will be involved. At later stages more involved themes such as clinical data and pricing/reimbursement issues come into focus, this requires more fields of expertise and so the investigation will balloon to surprisingly large numbers – you may see teams of 40 people or more.

The investigation team will involve a mix of employees from the investigating firm and external consultants. Consultants are most often used when the investing company is inexperienced in the technology being investigated. Venture capital firms may outsource all of the investigation to consultants, leaving their time free for deal flow and final investment decisions. The company will perform a review of the conclusions but will (usually) trust the work of the hired experts.

Consultants are not only hired by large pharma or venture capital firms looking to perform a due diligence investigation, however. Many a small biotech company will hire a consultant to help prepare for the investigation – the consultant may help get their documents in order or simply help prepare a convincing summary of the results.

As mentioned, the composition of the team will vary widely depending on the complexity of the licensing arrangement and will be split into different roles with different responsibilities. Accounting will analyse financial data, lawyers will determine the legal repercussions, smaller tasks will be outsourced to consultants, a central group will co-ordinate the entire process. The scientific experts will make up a sub-team of this larger effort and will, as you would expect, focus on assessment of the scientific factors.

The on-site team will usually work in the same room, focusing on their respective areas of expertise. It is important to take regular breaks to compare notes, summarise findings, and alert each other to potential problems.

Organisational tasks

As with everything in life, being organised will make things run smoother. Before you arrive at the site, there are a few things that you should cross-check and prepare.

Sign necessary confidentiality agreements

You don't *have* to have confidentiality agreements in place, but it is almost always a good idea. This provides both sides of the investigation with the reassurance that they can speak openly on topics which arise. Failing to have confidentiality agreements in place inevitably leads to circular conversations as each side attempts to say *just* enough to get a point across, but not so much that they get in trouble for spilling secrets. Save yourself a lot of pain and get these in place.

Obtain authority and resources

Due diligence investigations require the investment of a significant amount of time and effort from multiple people. Before you begin, be certain that you have access to the financial and human resources required to complete the investigation. Be aware that you will often have tight timelines to finish everything – either your own company will want a fast deal or the other will want you out of their hair. Take this into account when planning the required manpower.

Next, ensure that you or the team leader have the required *authority* to conduct the investigation, preferably delegated with support from upper management. It is incredibly frustrating to realise after the investigation that management (a) has no idea what you are doing, and (b) will ignore your recommendations due to a lack of interest. Be sure that the required support is in place before the investigation begins!

Obtain access to virtual data rooms

The traditional approach to due diligence involves on-site investigation of confidential documents. This usually involves the respective parties emailing non-confidential documents back and forth prior to the in-depth investigation. This on-site will be held in a secure 'data room' to ensure that the confidential information is not lost or stolen. The room will hold matched experts from either side, so that the investigators can easily ask questions of someone with equivalent knowledge.

This set-up requires a significant amount of time and money, the investigators will need to take over a physical room for several days while monopolising the time of various employees. To try and minimise these costs, companies are turning towards virtual data rooms, electronic databases with controlled access for investigators.

There are two types of these electronic databases. The first comprises a computer physically present in the data room, with a secure access to the corporate server. These replace hardcopy print-outs rather than allowing off-site access, and are limited in the number of users that can use the system simultaneously. The second is a remote-access database, the 'virtual data room', in which a secure connection and log-on allows controlled access to these confidential documents from outside. Databases may be hosted by the company itself or via a third party, this is more common for small biotech firms which do not have extensive IT support.

The advantage of a virtual data room is that it allows a direct, secure connection – there is no emailing of confidential documents over non-secure connections. Multiple documents can be loaded up and the access to each controlled via log-on restrictions. This makes it very useful when several buyers are conducting simultaneous investigations. It also requires less travel from the auditing group.

The disadvantages mostly stem from the electronic nature of the format. Foremost is the lack of corresponding experts to help explain the documents – there will often be problems that come up that could easily be explained in a face-to-face meeting, but not over email. Similarly the chore of comparing multiple documents, in different formats, over an often-unreliable connection can make due diligence a major pain.

Prepare your checklist

The majority of due diligence work will be the checking of confidential documents belonging to the licensor company. As these documents are confidential, this check will be done in a controlled environment – usually in a specific room at the technology-holder's location. You will be investigating and checking a large number of documents and information within a short amount of time. The best practice approach is thus to plan ahead and work from a checklist. The checklist ensures that you cover all the important factors and avoid missing anything in the stress of the investigation.

At the start of the investigation you should make a few preliminary requests to get the process started.

- Who will be available from the licensor company to find documents and answer questions?
- Which documents are considered confidential, and which documents can be removed from the site for checking later?
- What format will the documents be in? Electronic or printed?

From this point you will move into more specific requests relating to your focus of investigation. There are a number of areas which will be covered during due diligence. The licensor will likely have a number of 'marketing documents' designed for investors and the public. These are useful but should be considered biased, they will provide an overly favourable outlook.

More useful information will be found in official source documents and internal study reports. There are, naturally, many different documents which need to be checked, often an overwhelming number. You should thus aim to arrive at the on-site investigation with your own checklist of action items to work through. Every investigation and every specialisation will have their own focus and so their own list of items, however a generalised example can be found at the end of this book.

These will be covered in further detail in the following sections, but a brief overview of documents you might request include:

- Regulatory correspondence or dossier sections
- Investigator brochures
- Preclinical and clinical study reports
- Scientific publications
- Internal study reports
- Investigational new drug applications
- CMC or supply chain documents, reports and plans
- Marketing documents (brand plans, primary and secondary market research, competitor intelligence)

Regardless of the contents, a checklist is extremely useful for any investigator. The due diligence process is busy, stressful and often chaotic – a list will help you keep yourself organised and ensure that no important points are missed. It also serves as a handy marker of how much you have left to check. Having said that, you should be flexible enough to drop the list and chase down other items which come up. This is why you should always inform your team members directly if something appears to be a problem – the information may help them see otherwise hidden aspects of the problem.

It is also best to have a location to index and record documents as you receive them. Feel free to come back later to investigate them further, but you should at least note documents which have been received. As there will be many documents involved during the several days you are there, this helps you to keep an overview of what has been checked and what remains to be requested.

Specialist areas

Each expert will have their own area of specialisation and thus their own focus during the due diligence investigation. The typical experts involved in the scientific due diligence assessment are described in the following list, further details on what they should be assessing is provided in the sections referenced.

- Regulatory affairs
- Quality
- Chemistry, manufacturing and controls
- Preclinical studies
- Clinical studies
- Marketing
- Intellectual property

For more information on each focus area, turn to the appropriate section.

Chapter 4. Regulatory affairs

If there is one constant in the pharmaceutical industry, it is regulations. The early days of medicine were characterised by quack treatments, impure mixtures, dangerous drugs, and a number of dead patients. Society demanded, quite sensibly, that their medicine be safe and effective and so something needed to be done. The result was an ever-stricter set of rules and regulations designed to ensure medical safety, with tighter laws being passed each time a new set of patient deaths occurred.

The end result of this is that getting a pharmaceutical to market requires meeting a number of stringent requirements – a multi-year process costing millions of dollars and requiring numerous back-and-forth communications with the regulatory authorities. If these requirements are not met then you cannot sell your new wonder-drug, which in turn leaves the investment in the dirt, another wasted opportunity in the pharmaceutical field. The regulatory affairs department and their associated documentation are thus vital for the success of any pharmaceutical.

What does this mean for your due diligence investigation? It means that regulatory affairs experts will be a core part of the scientific due diligence team, as they have the best overview of the requirements for obtaining marketing approval. Regulatory will be involved in an overall assessment of the applicable guidelines, the data generated, the CMC/supply strategy, and the strengths and weaknesses of the drug. They review the regulatory strategy and clinical study plan, identify alternative pathways for approval, and examine the existing regulatory applications. Most importantly, they will provide an estimate as to whether the data is likely to support the final approval of the drug.

So what sort of things do you need to look out for when performing regulatory due diligence?

- Are the development plan and data gathered likely to suffice for marketing authorisation?
- Has the pathway to approval has been mapped out?
- For already-approved drugs, do the lifecycle management requirements match the benefits?
- Do special circumstances requiring deeper investigation exist?

The development plan and available data

Although ‘development’ can be considered as covering the entire process of taking a drug through to market authorisation, many draw a line between the development prior to clinical trials and the clinical trials themselves. This ‘prior’ work may include *in vitro* experiments, cell culture studies, and animal experiments. This part of the process is usually the most familiar to those coming from academia, as it matches many approaches used in university research. Indeed, many companies at this stage are often **spin-off companies** set up by academic entrepreneurs with a focus on commercialising a new technology or target identified during their own basic research work.

Most pharmaceutical development programs will follow a roughly similar progression. A target biochemical pathway will be identified. A drug which binds to the target is found, usually by **screening** (trialling many thousands of options to identify those which have an acceptable affinity for the target). The successes from this stage, known as **hits**, will then be modified to improve their attributes – small molecules will have differing functional groups swapped around, biologicals will undergo rounds of targeted mutagenesis. This occurs alongside a series of *in vitro* and *ex vivo* (cell-culture-based) tests for efficacy and toxicity, normally involving multiple rounds of testing, improvement, testing again, etc.

Many compounds will be discarded at this stage and many projects will be outright cancelled. Research projects will be ruthlessly cut if they do not appear to be making progress or if the market conditions are no longer favourable, based on the general philosophy that it is better to cut a program too early than too late. Identified **lead compounds** will be brought through to animal studies, known

as **pre-clinical testing**. Drugs normally need to be tested on mice and a second model species (which acts as a surrogate for the disease) prior to going into human trials. The number of compounds under investigation will fall dramatically with each succeeding stage of drug development. Of the thousands of candidate molecules which enter the development pipeline a tiny fraction will survive to reach regulatory approval and sale on the market.

Clinical trial applications

Before any drug can be sold on the market, it needs to be approved by regulatory health authorities such as the US Food and Drug Administration. Obtaining this approval is a long and complicated procedure, one in which the safety, efficacy and reliability of both the drug and the manufacturing process need to be proved many times over. This is done via regulatory submissions, which occur at many stages during the development process. The most important of these, however, occur before gaining clinical trial authorisation and before marketing authorisation. These are therefore important areas to examine when performing scientific due diligence.

Any new drug must be proved to be effective and safe in humans, this is achieved using a series of clinical trials. Before this can occur, however, the company needs to obtain approval to actually run the trials. Information from preclinical and biochemical studies is gathered together and used by regulatory affairs to write the clinical trial applications, known as an Investigational New Drug (IND) dossier in the US, an Investigational Medicinal Product Documentation (IMPD) in the EU and a Clinical Trial Exemption (CTX) in the UK. We cover important factors relating to clinical trials in a later section, however a few points also apply here.

Clinical trial application documentation provides a detailed overview of the information obtained during preliminary development and preclinical (animal) trials. Submission of an application will almost always trigger **Requests for Information** from the authority, in which they will demand clarification or further data on certain topics. The initial submission, requests for information, and associated answers are all important for the purposes of scientific due diligence. How comprehensive is the data package available? What were the regulatory authority responses like? Did they seem supportive, hostile, indifferent? Can you spot gaps in the development process so far based on the regulatory responses? Are there requests which were not completely answered and thus could represent a problem for later submissions?

Very few clinical trials will measure if the drug ‘cures’ a disease, as this is a relatively difficult thing to prove and leads to highly variable outcomes. Instead the trial will look at a **surrogate endpoint**, a biological variable which is *related* to disease progression but far easier to determine. Does this surrogate endpoint make sense? Would it actually be accepted by the regulatory authority? Are there precedents for these endpoints in other clinical trials which you can use to argue your case? This is where the multitude of openly available information from regulatory databases comes into play. Sources such as the US **ClinicalTrials.gov** or **Drugs@FDA** databases, or the **European Public Assessment Reports** provide information on current clinical trials or approved drugs – this allows you to determine the current state of regulator thinking and precedents in place.

Documentation

Regulatory requirements force pharmaceutical companies to document everything. Indeed there is a standard saying the world of pharmaceuticals, “if it wasn’t documented, it wasn’t done”. This means that even the shortest of development programs will need to produce reams of paper reports and documents – a problem which only gets worse as development continues.

Progress through the development pathway is recorded and organised by development reports and development protocols. The overarching plan will be recorded in a document often known as the development master plan, a listing of all the experiments which will be needed to reach the end goal. You should remember the plan for *continuing* development is just as important as the results from development *so far* – and so any scientific due diligence assessment will need to examine the

development plan for upcoming experiments. Does this plan make sense? Are the required experiments included in the listing, or are there gaps which regulatory authorities will want to see filled? What are the timelines for these experiments? Do these seem reasonable?

Answering these questions means that you will need to verify the existence and completeness of the development documents. Although every project is different, there will usually be several key documents that are produced along the way. Missing documents are usually a bad sign, implying that the company being investigated has skipped one or two steps in the development process. Many due diligence investigators will use lists of typical development documents as a checklist for completeness. An example list is provided in the Appendix.

It is also important to check the regulatory documents which have been put together for the submission. The standard method of submitting information to the authorities is via the **dossier**, which is itself usually patterned on the **Common Technical Document** format. This dossier is based on the source documents mentioned previously, it is therefore vitally important to check that the *information in the dossier matches the information in the source documents*. It is very easy for information to be incorrectly transcribed or not updated in line with the source document – this will create a gap in the regulatory submission that can be very difficult to fix and may lead to incompliance or recalls.

Obtaining approval

Before a drug can be sold on the market in a country or region it must be approved by the government health authority. Obtaining this approval can be very difficult or quite simple, depending on the amount of data you have and the novelty of the drug in question.

At one end of the novelty scale are generic drugs, copies of off-patent drugs which have already been approved by the authorities, often years before. As these drugs already have a long history of use in patients the generic manufacturer only needs to show that their copy is chemically and pharmacologically equivalent – a fairly simple set of clinical trials and thus relatively low risk. This can be contrasted with a New Chemical Entity, a drug in which no active part of the molecule has been previously approved by the health authority – i.e. it is a completely new drug. These untried molecules must be thoroughly tested for safety and efficacy via a number of clinical and preclinical trials.

Regardless of generic or new chemical entity, the results from these studies must be convincing to the health authorities. New drugs are considered to be risky and thus the marketing authorisation application will receive many more questions regarding efficacy measures, adverse events during studies, complicated questions on the details of manufacturing, etc. You will need to keep this heightened scrutiny in mind while performing scientific due diligence – be sure that any new, risky drugs have sufficient underlying data to pass the approval process.

Most importantly, does the proposed development plan match up with health authority guidance? Guidance documents are published by health authorities to provide a written explanation of their thinking on a topic. Guidance documents can be broad (e.g. covering expectations for clinical trial documentation) or very specific (e.g. the allowable cases for repackaging of biological drugs). Regardless of the topic, authority guidance is extremely important. It is assumed that a pharmaceutical company will be working in accordance with the guidance recommendations as these are considered best practice. If you (or the company you are investigating) want to go against the guidance recommendations, there had better be a good scientific basis for your decision. Many health authority guidance documents are based on the harmonised publications of the ICH, making them a good starting point. A listing of the currently available ICH guidelines is provided in the Appendix.

Centralised versus mutual recognition procedure

The European Union (EU) is a major market for pharmaceuticals and a typical first or second step in the global roll-out of a drug. There are two major pathways by which drugs are approved for the European Union (i.e. the entire EU, rather than in one of the individual countries). These are known as the **centralised procedure** and the **mutual recognition procedure**. As part of the due diligence process, it is important to determine which regulatory approach is the best for the product. Is the company following the ideal approach? If not, why not?

The centralised procedure allows the applicant to make a single submission which, when approved, is considered valid for the entire EU. It therefore saves time and regulatory efforts, but does require that you have the same **marketing authorisation holder** and **trademark** in every EU member state. The centralised procedure is compulsory for biotech products, orphan drugs, and drugs targeting cancer, AIDS and neurodegenerative diseases – it can also be chosen voluntarily by companies with newer pharmaceuticals.

The mutual recognition procedure is slightly more complicated. A drug must first be approved in a single member state, this is then known as the reference member state. Following approval, the evaluation and concerns of the reference member is passed on to other countries within the EU, these are known as concerned member states. These are then asked to 'mutually recognise' the approval of the drug – if they agree then the drug is considered to be approved for sale in all agreeing countries. A closely related variant is known as the decentralised procedure, which follows the same steps but which is only available for drugs which have not yet been approved in any EU country. The advantage of these approaches is flexibility – the trademark and marketing holder may be varied between different EU countries as needed. The disadvantage, of course, is the longer and more complex path to full approval.

One factor which is specific to the European Union is the splitting of approval roles between the different countries of the union. Drugs approved via the centralised procedure are assessed by representatives of two member nations, known as the Rapporteur and Co-rapporteur. These roles are not compulsory, which means that the applicant essentially needs to convince people in the pool of potential rapporteurs that their drug is worth reviewing. Drugs approved via the mutual recognition procedure are first assessed by a single Reference Member State and then approved in further countries. As with the role of rapporteur, a company must be able to convince the member state health authorities that their project is worth taking on. Thus a company with a promising candidate drug will often start speaking to potential reviewers even before clinical trials begin – essentially a marketing tour to raise interest. As a due diligence auditor, you should be checking if this process has begun – has a rapporteur or reference member state been identified? Has anyone expressed interest in the role? Does the company even have a plan for approval?

Scientific advice meetings

As part of the regulatory submission process, the applicant company is given the chance to discuss or meet with the health authority to discuss the specifics of their development or regulatory strategy. There are a number of these advice meetings and they are targeted towards different stages of the development process. When dealing with an FDA application you will see references to pre-IND, end-of-phase-II, Type A, B, and C, carcinogenicity assessment meetings, or the pre-501(k) for devices; EMA provides various **Scientific Advice Meetings** as well.

In general, the applicant will present an overview of their project, specific information relating to an area under discussion, and then will ask for the opinion of the authority. For example, the company may present data covering variability of a particular impurity, and then ask: does the FDA agree that the described variability is acceptable? This will be provided in a written format before the meeting (known as a **Briefing Book**) and covered again during the meeting itself. Authority representatives

will normally give a preliminary response during the meeting itself and then 'officially' reply in writing at a later date.

You should ask for and review copies of all correspondence with health authorities such as the FDA or EMA. This includes official documents such as briefing books and unofficial documents such as internal meeting minutes. When doing so, remember that the unofficial documents may be biased towards the company's point of view. Global markets also mean that a single drug may be at different stages of development in different regions. This is often the case when health authorities require clinical trials in specific patient populations before approval – Japan is a typical example here. Because of this you should not blindly focus on FDA correspondence – check that of major authorities such as EMA, PMDA (Japan) or Health Canada.

Correspondence allows you to keep an overview of the progress of a drug towards approval. You should list correspondence dates and parties involved, this helps to create a timeline of the progression. These timelines are particularly helpful when dealing with a drug which has been transferred between several different license holders. For example, multiple licensing deals may lead to situations where US rights are granted to one company, EU rights to another, while the original start-up still has rights to the New Zealand market. This is exactly as frustrating to deal with as you would expect, so keep notes!

Some topics are more commonly brought up during scientific advice meetings than others. A few of these 'typical topics' include:

- The toxicology program and the results obtained (including the safe and effective dosing ranges)
- The design of upcoming clinical trials, including proposed clinical endpoints, as well as whether the proposed statistical approach will be acceptable
- Whether 'external' clinical data will be allowed (e.g. data from EU patients in a US submission)
- Whether additional studies need to be performed for special patient populations
- What sort of follow-up studies will be required after approval to show long-term safety

The recommendations of EMA and the FDA during these meetings are extremely important for the long-term success of the medication. In particular, any problems which they comment on must be answered or solved before the final application. As part of your due diligence check, you need to determine if the advice given by the authorities has been adequately addressed – this is usually a question which will be answered by several experts working in parallel. If not, then why not? Is there a sound scientific reason for following an alternate approach?

If multiple meetings with authorities have occurred, you should check the documentation and opinions provided for all of them. It is sadly quite common to see that one recommendation from the list has been overlooked or ignored, this will inevitably turn out to be the greatest source of problems later on.

Currently approved drugs

In some cases the drug in question will already have marketing approval and thus already be in production and sales. This situation can often be more complicated than developing a new drug, as you will be dealing with old documents and old dossier modules which may not have been updated for years. In these cases it is important to assess the quality of the dossier and the degree of work which will be required to bring the dossier to current standards.

Several factors should be kept in mind when dealing with currently approved drugs:

- The number of countries in which marketing approval has been granted. Global rollout procedures will often lead to drug approvals being granted in many smaller countries where your regulatory knowledge may be limited. Does your firm have the required expertise for these regions, or will additional help be required? Do you even have the required number of regulatory managers? Even routine dossier maintenance can quickly add up when 50+ countries are involved.

- The age of the dossier. Old products were often approved prior to the widespread acceptance of the CTD format and so may use unfamiliar dossier structures. Worse, the information present will often be based on source documents which have long since disappeared or rely heavily on 'know-how' rather than SOPs. These legacy products will cause major difficulties when an update to modern standards is required, a common requirement during tech transfer to a new manufacturers.

- The number of open variations and regulatory commitments. Every commercial process undergoes changes, many of these will need to be filed with regulatory authorities. An extensive backlog of commitments or changes may lead to serious workloads after acquisition, particularly when dealing with a globally-submitted dossier.

Special circumstances

Several special circumstances exist which may require closer attention during the due diligence process. Some, such as orphan drug designation, allow for faster application processes or increased protection. Others, such as prior withdrawals, may be warning signs of underlying problems. All should be thoroughly checked for their impact on the eventual registration.

Orphan drug designation

An **orphan drug** is one which is being targeted at a rare disease. The number of patients suffering from these diseases are too few to allow a 'normal' drug to turn a profit – the costs of development would outweigh the income from selling to the small market. To encourage the development of drugs against these rare diseases, governments create a number of incentives for pharmaceutical companies such as tax breaks, fee waivers, improved intellectual property rights, or even a voucher for accelerated regulatory review. This in turn means that an orphan drug designation is a common target for smaller biotech firms with one or two molecules in the drug pipeline.

If the company being investigated is aiming for an orphan drug designation, then you should check whether this is actually reasonable or not. Keep in mind that different countries have different ideas of what is 'rare'. A rare disease in the US is one which affects less than 200,000 patients, in the EU or Australia one which affects less than 1 in 2000 patients. The orphan drug designation will heavily affect the plans for a global rollout of the pharmaceutical and so it is important to check that a long-term plan has been put together.

It is also worth determining whether the company aims to apply for the FDA rare paediatric disease priority review voucher. This is granted to companies which successfully register a rate paediatric disease (i.e. a rare disease of children), the voucher provides accelerated regulatory review of a *different* product. Most importantly, the voucher can be sold to other pharmaceutical firms to use for their own products, essentially making it a way to speed up *any* regulatory application. The flexibility of this voucher makes it a valuable commodity – vouchers have been sold for prices approaching half a million dollars. The potential to obtain a priority review voucher is of definite interest to investors, and thus should be part of your scientific due diligence.

Accelerated approval

Although the regulatory approval process is clearly defined, there are also additional pathways which may speed up the journey to marketing authorisation. Fast track procedures, priority reviews and accelerated approval timelines can provide significant advantages to a company pressing for rapid

roll-out of their drugs. Rolling submission allows updates to be filed as new data comes in – this allows a particularly important or timely drug to get a jump on the usual submission process. Receiving these designations is heavily dependent on the quality and targeted indications of the drug in question, however if achieved they can significantly improve timelines to product launch.

A few examples of these options are described in the following sections.

Conditional approval (EU)
Early marketing authorisation may be granted for medicines which fulfil an 'unmet medical need', those which treat as-yet untreatable diseases and where the benefits seen in early clinical trials outweigh the risks. Conditional approval allows the drug to be marketed but requires a number of extra studies to be performed, while a renewal application must be performed each year. Once enough data has been collected the conditional approval is converted into a normal marketing authorisation.

Approval under exceptional circumstances (EU)
This is granted in cases where it is impossible to properly test safety and efficacy in clinical trials – usually in cases where the disease is extremely rare. Thus the main difference to Conditional Approval is that this data cannot be gathered *even after* authorisation. It leads to a different form of marketing authorisation with very heavy requirements for safety surveillance and reporting.

Accelerated assessment (EU)
Drugs which are highly innovative and of major interest to public health may be granted accelerated approval. Under this status the normal assessment procedure will be reduced from 210 days down to 150.

Accelerated approval (US)
Similar to conditional approval in the EU, the US program provides early approval for drugs treating life-threatening diseases that have already shown a good risk/benefit ratio. It allows approval based on a surrogate endpoint, thus significantly shortening overall timelines. As in the EU, further Phase IV studies will need to be performed to prove these clinical benefits after approval has been granted. Once the data is available, the drug will receive traditional approval.

Priority review designation (US)
Priority designation is given by the FDA to promising new drugs which may significantly improve current treatments. This focuses FDA resources on the review process and leads to faster timelines, usually saving approximately 40% of the total assessment time. The applicant company can request priority review, but the final decision will be made by the FDA.

Priority review will most often be granted to drugs which demonstrate a 'significant improvement', usually implying:

- evidence of increased effectiveness in treatment, prevention, or diagnosis of a condition;
- elimination or substantial reduction of an adverse event which limits treatment
- evidence of safety and effectiveness in a new subpopulation

Fast track designation (US)
Fast-track designation is designed for products which target serious unmet medical needs. It must be requested by the company and leads to a number of benefits, including:

- More frequent meetings with FDA to discuss the development plan and data needed to support drug approval
- More frequent written communication from FDA about scientific topics (e.g. clinical trial design, use of biomarkers)

- Eligibility for Accelerated Approval and Priority Review, if required criteria are met
- *Rolling Review*, where the drug company can submit completed sections of its Biologic License Application (BLA) or New Drug Application (NDA) one at a time rather than waiting for the entire dossier to be complete

Prior regulatory withdrawal

It is entirely possible that the drug you are investigating has already been submitted for marketing authorisation, but then either withdrawn by the company or rejected by the health authority. This is, obviously, not a good sign and so will often be downplayed or even hidden by the technology holder during due diligence. To avoid this possibility it is a good idea to cross-check the drug against the EMA and FDA withdrawal/rejection listings online.

If a withdrawal or rejection has occurred, you should attempt to gain all information possible about the event – in particular the *reason* for withdrawing. Withdrawal because the contract manufacturer was too busy to find a slot for the pre-approval inspection is less of a problem, withdrawal because the authority had serious objections to the safety results is something else entirely. Whether this factor then becomes a deal-killer during due diligence is dependent on the amount of risk the company is willing to take on.

Importation

The manufacture of modern drugs is a complex and expensive process, particularly for the increasingly-popular biological therapeutics. This complexity requires specialised facilities and knowledge which many pharmaceutical companies (particularly smaller ones) simply do not possess. As a result many firms will contract out the manufacturing process to other specialised contract manufacturers. Many of these are located outside the typical 'major markets' of the US and EU, with India in particular having a very advanced contract manufacturing environment.

The cheaper manufacturing possible overseas has led many pharmaceutical companies to outsource production. This process does have its disadvantages, including the challenge of getting the process up and validated in an unfamiliar country. Returning the product to your home country can also be challenging, you need to ensure that the appropriate import requirements are met (lest your drug be held at the border by customs). This will usually require that a GMP inspection of the manufacturer has been performed by the FDA or EMA, ensure that this has either occurred or is in the planning stage. If your drug is imported for final packaging or processing, ensure that the GMP certificate of the final processing plant allows the use of imported material. And finally, be aware that mutual recognition of inspections between EMA and the FDA is tenuous at times – just because a site is allowed to export to the US does not automatically mean that they can export to other countries.

Chapter 5. Quality

Quality' is one of the most important words in the world of pharmaceuticals, with many millions of dollars and thousands of hours spent ensuring that the manufactured drug is as good as it can be. Listing all of the quality requirements for pharmaceutical manufacture could fill another book (or two) but there are several basic themes which will arise during due diligence. Many of these will revolve around the field of GxP.

GxP stands for Good 'x' Practice, a general term which encompasses Good Manufacturing Practice (GMP), Good Laboratory Practice (GLP), Good Clinical Practice (GCP), and many others. GxP guidelines are set in place to ensure that work is being done to a certain level of quality. The main components of any GxP guideline are traceability (can you follow what has been done?) and accountability (do you know who did it?), two factors which inevitably lead to lots and lots of documentation. The typical saying is "if it wasn't documented, it wasn't done" – you always need to have documented proof that a process or study was performed.

In general compliance to Good Manufacturing Practice is the most important factor for pharmaceuticals, it is an absolute requirement for drugs being produced for the market. However compliance with Good Laboratory Practice and Good Clinical Practice are also extremely important for persuading authorities that the development studies have provided accurate and reliable results.

GxP requirements force the implementation of quality assurance systems and processes into all aspects of the pharmaceutical development process – from initial compound screening through to the final commercial product. The importance of quality assurance therefore makes it a natural focus for the scientific due diligence investigators. An expert in quality assurance should examine the systems which are in place at the company being investigated (as well as those in place at their contractors). This review helps to determine if the current system is up to the required standards, or whether further processes need to be put in. Smaller firms or start-ups commonly have a more haphazard approach to quality when compared to the large pharmaceutical companies. As such there will usually be one or two new measures to be implemented.

The easiest way to start the quality investigation is with the help of inspection reports from previous audits. If failures in quality control have been noted, these will generally be noted in the audit report or even highlighted as a finding. Keep in mind that the lack of such a finding does *not necessarily* imply that there are no problems – the auditor may simply have missed the problem area during their inspection.

Good manufacturing practice

All products for human use should be manufactured under **Good Manufacturing Practice** (GMP) conditions. There are a few basic rules which underlie the entire field of GMP:

- Design the facility and processes correctly from the beginning
- Validate all processes in use
- Write down procedures, and follow them
- Identify who does what
- Keep detailed records
- Train the staff in their roles and processes
- Practice good hygiene

- Maintain the facilities and equipment
- Design quality control into the entire process
- Perform regular audits

Naturally there is more to GMP than this, it is a major field which employs many thousands of experts. A few areas are of greater importance and so should be specifically checked in the course of the due diligence investigation.

Has the company officially confirmed that they work according to GMP conditions? Be sure to check that the manufacturing site has a valid GMP Certificate stating that it has been approved to manufacture GMP-compliant goods. A statement regarding GMP compliance should be present in the regulatory dossier. This statement should also be signed by the **Qualified Person** (QP), who is the final point of quality control for a product. The QP is held personally liable for failures in the product and so will only sign off on the batch release when completely sure of the quality level.

Does the company being investigated work according to **standard operating procedures** (SOPs)? These ensure that the work being performed is done the same way each time and are an essential basis for all high-quality, reliable work. You should always request a list of SOPs from the company being investigated – do these SOPs cover the manufacturing process? The cleaning procedures? The qualification of equipment and personnel? If there are gaps, why is no SOP in use? Just as importantly, are they stored somewhere in a controlled environment (e.g. a read-only database with rules regarding who can update SOPs). Typical SOPs which should be present are discussed later in the book.

Does the company undergo regular **audits**? Regulatory authorities will regularly audit pharmaceutical companies to determine if they are working correctly – passing an audit from the FDA or EMA is a fundamental requirement prior to manufacturing drugs for the market. To prepare for this, companies will also perform **self-audits**, an inspection of the company by auditors working for or contracted to the company itself. This is considered a 'trial run', findings from internal auditors will require correction but will not have the wide-reaching consequences that an FDA finding will. In general, you should see a history of regular audits, both internal and external. If this is missing, you should ask for further information.

Does the company use external contractors? Are these contractors working under the same quality requirements as the parent company? How do you know? Ideally there will be contractual agreements in place setting out precisely what work will be done under what conditions. This is usually performed using a **quality agreement**, a comprehensive agreement covering each party's responsibilities for compliance with GMP. Be sure to review these agreements to ensure that the required standards are followed in all cases.

Typical GMP documents

There are several 'typical' GMP documents which you will come across in the course of a scientific due diligence investigation. The most important of these are usually batch records and SOPs, however you may come across all of the following:

- The *Quality Manual* describes the regulations which the company or department is required to follow
- *Policies* are more generalised documents which describe how specific aspects of GMP (e.g. documentation) will be implemented but will not provide details of how this is done.
- *Standard operating procedures* (usually known as SOPs) will provide step-by-step instructions for performing a specific process or activity.

- *Batch records* are used by the manufacturing department. They provide very detailed step-by-step instructions to perform an activity (e.g. manufacturing your drug) and contain space for measurements and activities to be recorded directly into the document. The blank document is known as a **master batch record**, it is filled in during the manufacturing process to create an **executed batch record**.

- *Test methods* are similar to SOPs in that they provide step-by-step instructions for the testing of materials, products, intermediates, environmental samples, etc. They have some similarities to batch records, in that they are filled in during the course of analysis to document the results of the testing process. Test methods are under the responsibility of the quality control department.

- *Specifications* provide the requirements that a raw material or product must meet before it can be used or sold. The results of the analytical testing will be compared to the set specifications by the quality control department, failure to meet specifications will normally lead to an investigation.

- *Logbooks* are normally used to record repeating tasks such as operation or maintenance of a piece of equipment. They may also be used to record activities such as clean room monitoring or preparation of solutions.

Batch records

Batch records are essential for reliable manufacturing of the drug itself. The specifics of the document will vary with the process – a packaging batch record will naturally have different steps than a manufacturing batch record. However several constants will be found on every batch record:

- A site for the unique batch or identification number, which will unambiguously identify which batch the record refers to.

- The quantities of materials being used for manufacturing

- Dates and times for process steps

- Details of the process steps being carried out, with descriptions of each action being performed

- Identity numbers for equipment being used

- Results of process parameters or in-process controls

- Tick-boxes for marking off completed steps

- Names and signatures of the people who are performing the tasks, as well as of their supervisors

You should assess whether the batch record provides a clear, unambiguous description of what should be done at each step. Is there sufficient information present? Is there sufficient space for observations and measurements to be recorded? If examining an executed record, was this information included, or are there gaps in the record? Did someone sign off on every page and (ideally) on every measurement or step? Is there a corresponding page which allows initials and signatures to be matched to individuals? Are all the pages present in the document?

Many regulatory authorities are beginning to require copies of batch records (either executed or master) during submissions. Similarly, the documents are a common topic during authority audits. As such you should be sure that the batch records are sufficient to support the eventual commercial manufacturing process.

Standard operating procedures

The investigation should check for the availability of **standard operating procedures** (SOPs). SOPs are an essential part of the quality system, a way to ensure that work is done in a consistent manner. They *should* exist for all aspects of the development, manufacturing, and nonclinical/clinical testing process. A large pharmaceutical firm with a strong quality focus will have thousands of SOPs covering almost every process imaginable. A small start-up firm is usually much less rigorous – they will have one or two covering their most important processes and plan to make more any week now, honestly.

Regardless of the company being investigated, you should examine the available SOPs. Are they detailed enough to provide a strict, easily-followed set of instructions? Or are they relatively broad and thus able to provide the people performing them with a lot of leeway? This is often the case (people prefer the chance to be flexible, after all), but will usually lead to different employees doing the same task in different ways. This in turn leads to inconsistent processes and eventual quality problems.

If you have the time, then dig deeper. Do the SOPs follow the relevant guidelines? Was the development work done according to the SOPs? Although you will rarely have time to go into the details of the SOPs during an investigation, it may help to keep an overview of the most important SOPs which should be in place.

The 'typical' SOPs can be roughly divided into several major areas:

Training and documentation

Training and documentation are vital for the knowledge of the employees and the smooth running of the plant. These SOPs will cover the processes to:

- Define the roles and responsibilities of all personnel working in the organization
- Prepare documents (e.g. SOPs), perform reviews to ensure accuracy, ensure approval by QA/ management, train workers on the SOP, distribute to those who need it, control the versions, and store/archive old versions
- Perform periodic review of documents to ensure that they fulfil current industrial practices and pharmacopoeia requirements
- Ensure that old documents are retired and archived
- Handle electronic records and signed documents (such as executed batch records), including archival, retrieval, and storage
- Perform electronic signatures of documents
- Create and control equipment logs

Cleaning and sanitisation

Cleanliness is extremely important in pharmaceutical manufacturing and is the source of many audit findings. SOPs here will cover processes needed for:

- Cleaning or sanitisation of equipment, facilities, and personnel
- Avoiding cross-contamination between different products
- Validating cleaning methods
- Cleaning between batches or between different products, including the verification that this process works

Manufacturing
Manufacturing and testing the product in question is not a simple matter and will normally be the subject of multiple different documents. SOPs will cover topics such as:

- Preparing the process validation protocol and reports
- Preparing master batch records
- Defining and implementing specifications for any particular product, raw material or other chemical
- Allocating a batch number to any particular batch
- Releasing a batch for further use or for sale to the market
- 'Incoming goods testing' to check raw and packaging materials after delivery
- Preparation and control of quality control data sheets, analytical methods and specifications
- Cross-checking/review of analytical data
- Performing stability testing

Investigating problems
Problems will always occur, regardless of the level of quality control, and thus it is vital that systems are in place to catch these when they occur. This includes systems for implementing changes to prevent these problems from reoccurring. SOPs will include:

- Investigation of OOS results
- Change control, the process for assessing the impact of any intended change to processes, documents, facilities or equipment
- Handling deviations, including the investigation itself and the provision of corrective and preventive actions (CAPAs)

Change control
Processes will always change over time, in major or minor ways. The experts in production and development think of better ways to make something, a supplier of plastic bottles will require replacing, the supplier stays the same but the plastic bottle manufacturing site will change, etc. etc. Each of these changes can and will occur.

Because process changes are inevitable, every pharmaceutical company should have systems in place to identify, evaluate, and implement these changes. This is a multi-step process: beginning with change *evaluation* (assessment and evaluation), then requiring *notification* (informing health authorities and customers of the change), waiting for *approval* (if necessary), and then finally *implementation* (implementing the planned change). Together this is known as **change control**.

Prospective changes will be evaluated by multiple departments within the pharmaceutical company. As every change is different the experts required for evaluation will also differ from change evaluation to change evaluation. In general, however, quality assurance and regulatory affairs will be required to assess the majority of prospective changes. Based on the evaluations of the experts, a group representing upper management within the company will decide if the change should go ahead.

From a due diligence point of view, it is likely that the company being investigated is using a contract manufacturer to produce their API and drug product. It is important to verify that the manufacturing site has adequate change control processes in place. More importantly, you should ensure that the

customer (i.e. you) will be informed *prior* to these changes occurring. Failure to communicate changes can lead to a number of compliance issues and occasionally product recalls due to regulatory failures – obviously things which should be avoided.

Good laboratory practice

Good laboratory practice (GLP) consists of a number of requirements to ensure the quality of developmental research. The guidelines do not cover clinical studies but instead focus on non-clinical experiments such as physico-chemical analytics or toxicity studies. As with the other GxP guidelines, good laboratory practice focuses on quality control and assurance throughout the scientific process. This includes requirements for thorough documentation, use of SOPs, equipment validation, facility requirements and the like. In many ways GLP is similar to GMP, although it requires less oversight from quality assurance in the daily work. In GMP, the quality group must sign off on all aspects of manufacturing, in GLP they tend to have a role which is more focused on inspections and auditing.

GLP was initially implemented in response to the unearthing of stunning failures in laboratory experiments performed by a commercial safety testing laboratory. Designed to ensure that all following work would be reliable and correct, GLP can be considered a minimum requirement for scientific development in the pharmaceutical world. Many small companies are based on academic research, this is very rarely performed under GLP conditions. However you should ensure that all 'serious' development work (after spin-off from the university lab) has been performed according to GLP.

Good clinical practice

The GxP equivalent for clinical studies is known as **good clinical practice** (GCP), a series of rules which cover the planning, documentation and running of a trial. There are many regulations in GCP, but the most important cover the requirement to ensure that research is scientifically accurate and comprehensively documented. Ethical considerations are also included – i.e. the rules requiring informed consent, safety of patients, however these are not as comprehensive as those in the more-often referenced Declaration of Helsinki.

As with GMP, GCP is verified through regular audits of the clinical trial organisation. It is therefore important for you as an auditor to have proof that the studies were done according to GCP. Ideally this will also include copies of audit investigational reports – although this is often considered confidential by the contract organisation and so may be difficult to obtain.

Chapter 6. Chemistry, Manufacturing and Controls

It is impossible to test a promising new therapeutic compound without actually *having* that promising new therapeutic compound. Thus it is vital that a method be in place to make that new compound, whether it be a small molecular entity or a hefty engineered antibody. Regardless of the drug in question, the ability to reliably and safely manufacture it is a basic requirement for any development program, and one which should be worked out in excruciating detail before clinical trials are started. This field of manufacturing is usually referred to as that of **chemistry, manufacturing and controls** (CMC).

CMC is a complex field, one in which many different experts need to work together to produce a drug reliably, safely, and cost-effectively. You will be shown manufacturing instructions, batch records, purity profiles, degradation pathway assessments, analytical method validation reports, reference standard declarations, and many, many more documents. This can be dangerous, as the sheer number of different areas can lead you down a rabbit-hole of minor details with minimal importance to your due diligence.

To avoid these traps, due diligence investigators should instead focus on several important areas:

- The planned drug product
- The manufacturing site
- The manufacturing process
- The 'hidden' information in drug or active substance master files

The following sections will cover these four areas in greater detail.

The planned drug product

Obviously the most important area to investigate is the drug itself. There are many factors which need to be checked here, including:

- The active pharmaceutical ingredient
- The excipients
- Planned formulations and dosages
- Specifications of the materials and final product
- Stability profiles
- Changes from the investigational product

We cover these factors in further detail within the following sections.

The active pharmaceutical ingredient

The **active pharmaceutical ingredient** (or API) is the chemical or entity which actually causes the effect of the drug. This is different to **excipients**, chemicals which may modulate the attributes of the drug but which do not cause pharmacological changes. The structure of the API is determined well in advance of the majority of the development process – you can't test something if you don't know what it is, after all. Thus from a CMC point of view the main challenge is to produce a pure version of that API molecule with a minimum of cost and wasted material.

The important word here is *pure*, as the presence of impurities within the API can lead to reduced efficacy or even toxic effects. The purity of the API must be controlled with the appropriate

specifications and should, as a rule of thumb, be as pure as possible. Absolute purity is rarely possible and usually not cost effective. Instead it is important to determine *which* impurities are present and at what level. Toxicology assessments will then be performed to determine whether this is acceptable given the intended use of the drug.

Some forms of API do tend to cause more difficulties in manufacturing than others and so tend to attract more attention from regulatory authorities during the submission phase. In particular, any compound which has chirality, hygroscopy (water-absorbing properties), low solubility in water, mediocre stability, or light/temperature sensitivity will require extra checks during the manufacturing process. Authorities will expect you to be controlling for these potential problems and so this should be checked during the due diligence process.

One often-forgotten factor is that of availability, a particular problem for older products or ones which have been developed a while ago. The API is often produced by contract manufacturers, who make batches of material at times which are dependent on their availability and production schedule. You should ensure that the suppliers of key materials such as APIs (and excipients) are able to continue production of the API. Production capability should be verified both at the current level of manufacture and at the increased levels you expect once commercial manufacturing begins. Moving production to a new site is certainly possible (this is known as a **tech transfer**), however it is a complex and time-consuming process.

Excipients

Excipients are the 'other' chemicals within a drug, the ones which do not have a direct pharmacological effect but which ensure quality or modify the overall effect of the drug. Buffering agents are common excipients in liquid formulations, ensuring that pH-sensitive APIs remain at their correct pH values. Other typical excipients include bulking agents to add mass to a tablet, binders to hold everything together, flavours to mask horrible tastes, preservatives to prevent degradation, etc. etc.

The choice of excipients will be made during the development process and should be based on study results. In other words, a particular buffer should have been chosen because it is the most appropriate chemical in this system, not because it was lying around the laboratory. You should ensure that these studies have been performed and documented, with reasonable and persuasive results underlying the choice of excipient.

It is also important to check whether the excipients in use are 'standard' chemicals – ones which are included in relevant pharmacopeia and for which commonly agreed toxicity and purity assessments have been determined. Although it is possible to use a 'novel' excipient for your drug, the company must take responsibility for showing that the excipient is safe and well-manufactured. In practice this involves performing pre-clinical and clinical trials and providing a vast amount of information for the excipient – a similar process to filing a new API. Most companies will try to avoid using novel excipients in their drug formulation due to these heavy requirements and thus the due diligence process should check the status of excipients in use. If an excipient *does* need to be filed as a novel excipient, then you should ensure that the required data should be available or being generated. Keep in mind that an old excipient provided via a new route of administration is *still a novel excipient*. For example, an excipient commonly used in tablets will still need a full safety-data package when used in an injectable formulation.

Formulation and dosage

A pharmaceutical is more than just an active ingredient, it is a carefully designed mix of compounds provided in set amounts so as to control the bioavailability and stability of the whole. The **formulation** of the drug comprises the components – the amount of API, the amounts of excipients and fillers. The **dosage** represents the amount of drug which is being provided – drugs designed for

children have smaller dosages than those for adults, for example. The combination of dosage and formulation allows you to target the same active ingredient to different patients with different needs.

Early development projects rarely have the formulation and dosage requirements worked out. Instead you should focus on the *planned* form and indication. Will the physicochemical properties of the molecule allow you to develop a product with minimal problems? Are there properties which will prevent you using a certain route of administration (for example, biologicals are rarely acid-resistant and so cannot be taken orally)? Will this affect market acceptance? Does the market expect a certain dosage/efficacy level, and will you be able to supply this? Are there problems which may affect the overall formulation development plan?

Later projects which have reached clinical trials will have already determined the final dosage and formulation. In theory at least. You should always check whether changes have occurred since the development or preclinical studies – major changes to the formulation can often invalidate these results and leave you with a gap in the data. This gap can be closed through bioequivalence studies or other methods but it is better to avoid the difficulty from the start.

You should also look into future plans for new formulations. These will usually be targeted at subsections of the original patient population or at new patient groups. The typical example here is a paediatric dosage, reduced amounts of drug which are suitable for the (hopefully!) lower bodyweight of children. However you may find formulation changes are required to better address new indications or even country-specific requirements. Assess the likely development requirements to make these new dosages and formulations – what sort of additional costs will be incurred as a result?

Specifications of drug product and drug substance

The quality of the drug product and components are controlled through **specifications**, attributes of the item which are tested via analytical methods. These attributes must lie within the specified ranges for the material to be considered 'in spec' and thus ok for further use. Specifications will be set for every part of the pharmaceutical, from the raw materials to the packaging to the final product.

Specifications are usually set based on the variability of the product during manufacturing and development, combined with knowledge of the process reliability. During early development these will be fairly broad simply due to a lack of information – as more data is developed, the preliminary specifications will be firmed up and modified. You should check if the data which has been gathered is sufficient to set *meaningful* specifications, ones which are scientifically justifiable and which should (hopefully) correlate with ICH Q6A/Q6B guidelines. These will be documented in a specification sheet and used for regulatory filings and quality control.

These specifications play a vital part in controlling the quality of the pharmaceutical and thus should be thoroughly checked during the due diligence process. The most important questions are whether the specifications make sense and whether they were based on reasonable scientific data? Beyond this there are several specific areas to check.

Pharmacopeia

Specifications for 'commonly used' drugs and raw materials are set in **pharmacopeia**, extensive listings of requirements which are published by authorities in all of the major countries. The two major ones for pharmaceutical manufacture are the United States Pharmacopeia (USP) and European Pharmacopeia (Ph. Eur.). As a general rule, if a monograph for a particular chemical exists then you will be expected to match your specifications to one or the other of these. It should be verified that the specifications set by the company under investigation match with pharmacopeia requirements. If they do not match, then why? Can the reason be justified to health authorities?

Structure and degradation

It is a fairly reasonable assumption that you will know the molecular structure of your active pharmaceutical ingredient. Indeed your development team will have spent a significant amount of

time and effort finding the ideal molecule – it would be a major red flag if this knowledge was *not* present. Biologicals are slightly more complicated, their size and complexity combined with the biotech-based manufacturing processes mean that there is more variability in the structure (e.g. in protein glycosylation levels). In these cases you should know the primary structure of the protein as well as having defined narrow ranges for these variable structural parameters. If working with a more variable, heterogeneous protein (such as those coupled to hydrogels), then you should at least be able to define a typical range of structures.

As well as the structure, the development team should have determined the typical degradation pathways of the active ingredient. These degradation products will comprise the most common impurities and appropriate analytical tests should be established to detect these impurities. This allows you to monitor the quality of the material. Degradation pathways are considered important knowledge by health authorities and thus your due diligence check should ensure that they have been determined. You should further check to see if the analytical tests in place are capable of detecting these known degradation products. If so, how sensitive are they? Does the sensitivity allow you to detect potentially toxic degradation products?

Quality attributes

The early development work should have helped to define a **Quality Target Product Profile** (QTPP), a profile of the requirements that the final drug should have. This QTPP will take various factors into consideration, from the route of administration to bioavailability and stability. This information is closely linked to the definition of **Critical Quality Attributes**, the product attributes which will have the greatest effect on the quality of the final pharmaceutical. The control strategy for the manufacturing process will be designed with the aim of providing tight monitoring of these quality attributes and so focusing the analytical program on the most important variables.

You should determine whether the company being investigated has correctly identified their critical quality attributes. Have the results from previous experiments, risk assessments and prior knowledge been brought together to identify these attributes? Has the company linked variations in raw material attributes to final product quality? How about variation in the process steps? If yes, have they introduced additional control measures to account for this? Can all of the variability in product quality be linked to the identified attributes? If not, what further work needs to be performed to find the 'missing' sources of variability?

Analytical procedures

The measurement of specifications and other parameters is done using analytical methods, an important topic which is sadly often overlooked. It is not enough to simply measure a parameter, you must be certain that your measurement system is able to reliably deliver the correct result each time.

Analytical methods need to be **validated**, shown to work in a reliable way under controlled conditions. Method validation is performed according to typical standards laid down in pharmacopeia or ICH guidelines. In general you will want to see data covering system stability, precision, limits of detection and quantitation and specificity. It is important to check that the methods have been validated according to current standards – a method which was last validated a decade ago probably needs to be rechecked.

Pharmacopeia also set requirements for analytical testing – how it should be performed, which reagents should be used, what results should be expected. If you wish to claim compliance to a pharmacopeia for your specifications (which you should) then the analytical testing will also need to be done according to the pharmacopeia. This, therefore, is something else which will need to be checked during due diligence.

Stability profiles

The greatest drug in the world is useless if it decays a day after manufacture. This makes the stability profile of a drug very important for due diligence investigations, particularly with respect to the planned or registered storage conditions and acceptable shelf life. The allowable shelf life period has a direct impact on supply chain and marketing – the longer, the better.

To show that the drug can be stored for reasonable periods of time, a pharmaceutical company needs to perform **stability testing**. This involves storing a large number of samples of the drug substance or drug product at several different conditions. The stability of the drug is checked by removing samples at regular intervals and testing to see if the quality level is consistent.

These studies will be performed under different conditions, the most typical involving variations in temperature, humidity, and light exposure. All stability programs will test at the intended conditions (i.e. the correct storage temperature) for a period of time matching the intended shelf life. As this can require several years testing will also be conducted at accelerated conditions (i.e. higher temperature and humidity). These conditions increase the degradation rate of the product and so allow unexpected changes in quality to be observed within a reasonable amount of time. Light sensitivity testing is usually conducted separately and will rarely be repeated after initial development studies.

The quality level is checked via analytical testing, with a focus on attributes which may be affected by the storage process. Typically this includes purity, degradation products, and potential microbial contamination – however you should expect to see numerous others depending on the product quality attributes. As you would expect, testing should be performed using validated analytical methods.

From a due diligence point of view, you will find that the stage of development influences the amount of data available. Early projects will have limited stability data, those going into clinical trials are required to have several months of stability from large-scale batches. Check which stability studies have been started and which ones are planned. Is there any indication that the drug is sensitive to storage, or may undergo unwanted degradation? If yes, was it observed in intended or accelerated conditions? What is the planned shelf life? Is the data available sufficient to support the planned shelf life, or will you be running close to the edge of the relevant specifications? This may lead to problems after approval and the need to file shelf-life reductions – a serious problem for your long-term profitability.

Investigational medicinal products

An **investigational medicinal product** (IMP) is a pharmaceutical which will be used in a human clinical trial. This is *usually* a compound which is still in development, i.e. one which has not yet been granted marketing authorisation. However an approved product can also be considered an IMP if it is part of a clinical trial.

As the investigational product will be given to humans it needs to fulfil a number of requirements. The product must have been manufactured under Good Manufacturing Practice requirements according to a process which has been approved by the relevant health authorities. It must be tested according to the defined specifications, be free from unwanted impurities, and (in the EU) be certified by the appropriate Qualified Person. All of these processes and checks will be part of the dossier which is submitted for the **clinical trial application** (CTA).

The manufacturing process for the IMP may differ from that used in commercial production. However the quality and composition of the IMP drug must be the same as that intended for the market – i.e. you cannot perform a clinical trial with one formulation and then get approval for another. These results may be considered ‘supporting data’ for your actual submission, however.

Optimisation of the manufacturing process after the IMP production but prior to commercial manufacture is common and indeed desired by health authorities. As part of due diligence, you will be examining the risks and shortfalls of the current process. Alongside this you should determine if the

risks in the current process could be minimised by the addition of further controls or optimisation. If so, would the improved process be sufficient to receive marketing authorisation? Are further process characterisation studies required to reach this point? How expensive would those studies be?

The manufacturing site

Just as *what* drug is being made is *where* the drug is being made. Information on the manufacturing site, facilities and manufacturing environment is a required part of the regulatory submission. Sites which are not familiar to the health authorities will need to undergo a **pre-approval inspection** (PAI) in which a team of inspectors will descend on the facility for a rigorous and highly stressful audit. Failing this audit will prevent marketing approval from being obtained until the observed problems are fixed – this often requires a second round of auditing. As such the quality of the site is extremely important for the overall success of the therapeutic.

As mentioned in the Quality section, all manufacturing should be performed according to current **good manufacturing practice** (GMP). Drug substance or drug product manufactured in non-GMP-compliant premises, even if only used for pre-clinical work, is a very bad sign and one which often kills a deal. As an auditor you should even be wary of manufacturing sites which have never had an FDA or EMA audit. Audits are nerve-wracking but nonetheless demonstrate that the site understands what they are doing. Newer companies without previous inspections have a much higher chance of audit observations or findings during the pre-approval inspection for your drug.

A comprehensive overview of the manufacturing site may be found in the **site master file**. This document is prepared by the manufacturer as an overview of their facilities and processes. It is normally used as an internal reference, as an information source during audits, and provided to customers during contract agreements. This makes it an excellent document for obtaining an overview of the manufacturing facility when performing a due diligence investigation. If possible, request this document and use it for your initial check of the manufacturing options.

The exact content of the site master file will differ between companies, but in general you should expect to find the following information:

General information:

- Brief information on the firm
- Pharmaceutical manufacturing activities which are permitted by their licensing authority
- The type of products being manufactured, occasionally with flowcharts detailing procedure and process flow (this is rare however)
- A short description of the quality management system of the firm

Personnel:

- Number of employees engaged in the production, quality control, storage and distribution
- Qualification, experience, and responsibilities of key personnel

Premises:

- A simple floorplan or description of the manufacturing areas
- The nature of the construction (concrete, etc.) and fixtures/fittings
- A brief description of the ventilation systems with more details on critical areas with potential risk of airborne contamination.
- Cleanliness classification of the rooms used for the manufacture of sterile products (e.g. Zone A, Zone D, etc.)

- If present, a description of the special areas for the handling of highly toxic, hazardous, and sensitizing materials
- A brief description of the water system and sanitisation processes

Equipment:

- A brief description of major equipment used in production and in the quality control laboratories
- A description of the qualification, calibration and preventive maintenance programs for equipment

Sanitation:

- A brief description or a simple statement that written specifications and procedures for cleaning manufacturing areas and equipment exist

Production:

- A brief description of typical production operations which are performed in the facilities
- Either a description or a statement regarding the existence of SOPs for handling starting materials, packaging materials, and bulk and finished products
- Sometimes a brief description of the general policy for process validation will be included here

Quality control:

- A description of the quality control system and the activities undertaken by the quality control department.
- Sometimes this will include a description of release procedures for finished products.
- A short description of the self-inspection/self-audit system, the most important part of which is the information that an independent and experienced external expert does regular checks of GMP-compliance

The production process

The production process consists of multiple **process steps** linked together, each indicating a single action in the manufacturing process. Typical process steps include mixing compounds, filtration, adjusting pH levels, etc. Tests will be included throughout these steps to monitor the overall progression and quality of the process. These tests and measurements are known as **in-process controls** and **process parameters**.

The intermediate stages within a process will have a number of **quality attributes** (QAs), the properties or characteristics which affect the final product. These attributes are affected by variations in the process parameters (PPs), the measurable variables which occur during manufacturing. These process parameters are monitored by in-process controls (IPCs), the measurements and values that will be taken as the process continues. IPCs, PPs, and attributes are divided according to their criticality, split into the categories Critical, Key and Non-key. All of these IPCs and PPs will be listed in the master batch record but only a subset of these will be part of the regulatory application.

Manufacturing information unfortunately tends to be complex, highly detailed, and split across a number of documents. This can cause problems when time is short and the assessment needs to be made quickly, thus it is often helpful to take the overview present in the regulatory dossier. The highest level of information will be present in the final dossier but even earlier versions will have to

provide manufacturing information. These documents will contain an overview of the process, critical process parameters or in-process controls, and details of the manufacturers' license.

How do you know if a production process is up to scratch? This is a complex question to answer, one which requires familiarity with the current guidelines issued by health authorities such as the FDA, EMA, and ICH (a handily short acronym for the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use). ICH guidelines are considered 'harmonised', they are broadly applicable to all countries which are part of the international group of the US, EU, and Japan, plus others. ICH recommendations have been integrated or copied wholesale into the regulatory requirements of countries around the world. You should examine the manufacturing process and determine if the recommendations of recent ICH guidelines have been implemented, in particular Q7, Q8, Q9 and Q10 (for more information on ICH guidelines see the appendixes). There are, naturally, certain areas which you can focus your attention on. Is the active ingredient pure? Free of enantiomeric variants (molecular variants at chiral centres, a major problem in drugs since thalidomide)? Are the purity and other quality measures consistent from batch to batch? Have reasonable specifications and analytical methods been put in place to control that quality and have those methods been correctly validated?

As a general rule these checks should be performed regardless of whether the company makes its own drugs or outsources to a contract manufacturer. Outsourced manufacture is very common in smaller pharma companies and will make your investigation more difficult – expect to have problems obtaining detailed information which would be considered a commercial secret. In these cases it is very helpful to do a general check of the reputation of the contract manufacturer. Are they 'clean' or have they had issues with other companies in the past? Check for online reports of audits from the FDA, were any findings of 483 violations listed? If yes, have those findings been resolved? If no audits have yet been performed, why not?

Quality

All products for human use should be manufactured under Good Manufacturing Practice (GMP) conditions. GMP requirements and the quality assurance process are described in further detail in the quality chapter.

Quantity

One factor which is often overlooked is whether sufficient material is present for the required clinical and preclinical testing. A fairly small amount is needed for initial development steps, usually derived from a pilot-plant-scale manufacturing process. However even this material needs to come from *somewhere* – and thus your first question should be if the necessary material has been manufactured. If it has been made by a contract manufacturer in an external location, has the necessary import permission been granted?

If the material doesn't exist in the needed quantities then things become more complicated. Who will be making it? How long will it take them to do so? What effect will this have on the overall development timelines? Will it push back your critical path to marketing approval? If yes then what does that do to the business case?

Scale-up

Relatively small amounts of drug product are needed for development, process characterisation, and the clinical testing phase. Once a drug receives marketing approval, however, the company must produce multiple batches at commercial scale to keep up with the (hopefully) high demand. The change to larger-scale production is known as **scale-up** and it is significantly more complex than simply multiplying all the numbers by 100. Instead the larger process will need to assess altered mass flow, temperature equilibration, area/volume ratios, even stirring rates – none of which scale linearly when you move to a larger batch size.

This means that you will need to examine the current process with an eye for the eventual commercial-scale process. Can it be easily scaled to produce large levels of product? Are there unique steps or equipment which will make scale-up difficult? How much will production cost – a particularly important factor for expensive drugs such as biologicals? Can the planned commercial process and manufacturer provide enough drug product to keep up with the projected demand from customers?

Technology transfer

Many companies will perform a **technology transfer** to shift the manufacturing of a drug from one location to another. There are many reasons to perform a tech transfer. The new site may allow production of larger batches, it may involve lower costs, use newer technology, or even be located in a country which allows you to avoid patent disputes. A technology transfer is, however, a long and involved process. Suitable sites must be found, financial discussions held, legal agreements made, and audits performed. It will regularly take several years for the entire process to occur, making planning and project management a vital factor in their success.

For a successful transfer it must be shown that the drug produced at both sites can be considered equivalent. In other words, there must be no change in quality, purity, or efficacy. The manufacturing process itself must be essentially identical, with only slight changes in production steps or in-process controls. The process at the new site must be verified via **process validation**, with results from three large-scale batches showing consistent and reliable manufacture. The analytical tests present at each site must either be equivalent (if according to pharmacopeia) or cross-validated. Equivalence testing between the old and new drug material will also need to be performed.

In general, if the company being investigated is planning a technology transfer then they should also be planning these studies. If these are not in preparation then you should further question *why* they are not being performed. If the process is being modified in the course of the transfer, are there any risks associated with the modifications? Could these conceivably affect the quality of the final product? This is a known problem with the biological drugs, where even minor changes in process conditions can have far-reaching effects.

Process understanding / changes

Nothing ever works perfectly, drug manufacturing is no exception. For this reason it is important that the manufacturer has *process understanding* – knowledge of what happens at each step of manufacturing, how reliable this step is, what errors might occur, and how far the process can drift from the target parameters before the quality of the final product is affected. This understanding is supported by **process characterisation** experiments, which help determine just how far a process can be pushed while retaining the necessary level of quality.

In general the level of understanding is highest for 'familiar' manufacturing techniques and lowest for new or innovative ones which no-one has previously tried. You will want to assess the innovativeness of the method to determine potential risk, something which can be achieved in several ways. You may check ICH guidelines such as the Annex to ICH Q8 for typically-used manufacturing processes. You can perform searches of the literature for published descriptions of the process. Online searches may indicate other companies that have used similar methods. You can also check publically available regulatory reports such as the EU **European Public Assessment Report** (EPAR) or FDA public announcements. Identifying precedents for manufacturing is important for long-term success, as a general rule it is much easier to get marketing approval when working with well-established conditions.

As you would expect, experience performing a certain manufacturing process provides more information on its reliability and reproducibility. As knowledge grows over time, you will usually find that the manufacturing process planned during early development is far less efficient than the one which you eventually end up with. This is normal and you should not be surprised by process

changes. You should, however, ensure that any changes which were implemented were supported by scientific data and properly assessed through a change control system.

Process validation

Process validation is the act of showing that the commercial-scale manufacturing process consistently produces high-quality material. A validated process is an absolute requirement for producing pharmaceuticals for the market – no process validation, no product. Thus you should, naturally enough, verify the validation status of the process during due diligence. Pay particular attention to **deviations** and other mistakes which have occurred during the validation – why did they occur? Were the underlying problems identified and corrected? Have any changes been made to the manufacturing process which may make it 'different' to the validated one? If yes, can the process still be considered validated?

Beyond this, can the process be considered robust? Look at data from the in-process controls and release testing, check how they vary from batch to batch. You should also check for differences between the batches used for preclinical and clinical trials. Is there a lot of variation, or do the values stay consistently within a narrow range? If variation occurs, why is it happening? Which values are showing variation? This can be very important when looking at impurity profiles, as these can lead to differences in clinical efficacy. If variation exists, has the quality department conducted an investigation? If yes, what was the outcome and what are they doing to prevent it occurring again?

Environmental risk

In contrast to human safety risks, environmental impact tends to be comparatively ignored when thinking about new drugs. Despite this environmental factors are growing steadily more important for pharmaceuticals, environmental impact reports are often required to assess the use, storage, and disposal of the drug. Although the environmental impact of the manufacturing process is not part of the approval process, smart investigators will also check for problems which may occur here. Having your factory shut down for pollution problems (as has occurred in several locations over the years) will not help your long-term profitability in the slightest.

Hidden information

Manufacturing processes are rightly considered to be commercial secrets – small process improvements can have large effects on production costs when you are dealing with thousand-litre batch sizes. Due to its confidential nature, CMC information is rarely provided openly or ahead of time, thus you will usually first see it while at the on-site investigation. The details of manufacture may be further hidden behind **drug master files** or **active substance master files**. These are dossiers filed by the manufacturer with the FDA or EU, they provide a second layer of confidentiality by preventing the customer from knowing details about the contract manufacturer. We describe both in further detail below.

Drug Master File

The **Drug Master File (DMF)** is submitted to the FDA as a way to protect confidential information which may be required by client companies for their regulatory submission.

How does this work? Contract manufacturer Company A has a confidential process for producing a drug substance, excipient, packaging material, etc. Pharmaceutical Company B wishes to use material from Company A and intends to submit a regulatory dossier to receive marketing authorisation. Normally Company B would need to include detailed information on the manufacturing process to the health authority, but Company A does not want to share this information. Instead Company A files a DMF with the FDA, this contains all of the confidential details which the FDA would want to see during the submission process. Company B then submits their dossier with a **Letter of Authorisation**, a statement from Company A that they can *refer to* the details in the DMF. This allows Company B to complete their submission while retaining the confidential processes of Company A – a win for all concerned.

DMFs come in different types: Type II DMFs cover drug substances, intermediates, and drug products; Type III DMFs cover packaging materials; Type IV excipients, colourants and flavours; and Type V DMFs are more general reference information. Type I DMFs previously covered manufacturing sites, SOPs and personnel, but as of January 2000 are no longer accepted – the information is sometimes packaged into the newer Type V format.

There is no real 'open' or 'closed' part to a US DMF, instead it is up to the DMF-holding company to decide how much information they will share with their commercial partners. In extreme cases a Freedom of Information request may be used to obtain the information from the FDA itself – this is however a long and often unsuccessful process.

DMFs provide a number of new areas which need to be checked during due diligence. If the company being investigated is a DMF holder, then you should determine what type of DMF it is, whether it is 'active' or 'inactive', and whether the company has been providing the required updates to the FDA.

Most firms being investigated will be smaller biotech firms working with a DMF-holding contract manufacturer. The first question is to determine if the DMF is active. If yes, has your company been issued with a Letter of Authorisation? Do you have a copy of the DMF, or extracts thereof? This can provide you with information on the manufacturing process, including required raw materials, yields, and reliability. From here you can start estimating the quality of the process and thus whether changes will be needed prior to commercial manufacture.

Active substance master file

The **active substance master file** (ASMF) is the European equivalent to an FDA drug master file. It allows confidential information from the active substance manufacturer to be submitted to EMA directly. As with a DMF this can then be referred to by applicant companies without actually knowing what has been submitted. Thus the manufacturer protects their commercial secrets while allowing the marketing company to take full responsibility for the final drug. This last is important – although the manufacturer is actually making the active substance, it is up to the company selling the drug to make sure that everything is ok.

ASMFs are divided into an applicants' part and a restricted part. The restricted part contains all information which is considered confidential, it will never be shared with anyone outside EMA or state health authorities. The applicant's part is considered 'semi-open' – it does not contain confidential information but can only be shared with outside parties with the permission of the ASMF holder.

There are several drawbacks to the ASMF process. It is only applicable for the active substance (i.e. the actual drug molecule), there are no pathways present for packaging or excipients as in the US. Nor can it be used for biological active substances, which are considered to be too complex to be covered under the ASMF system. This severely limits its use for the majority of new drugs.

As with the DMF, an ASMF opens up a number of questions. How much information have you been provided from the applicant part of the ASMF? Have you an applicable letter of authorisation? Have references to the ASMF been correctly incorporated into the regulatory dossier?

Chapter 7. Preclinical studies

A prospective drug will need to be checked in animal experiments prior to testing in humans, a process which is termed **preclinical studies** or preclinical pharmacology. Preclinical work is a vital step on the road to market authorisation as the data developed during this stage underlies the clinical trial application – unreliable or unpersuasive data at this point can prevent a drug from moving forward to Phase I clinical trials. As such the preclinical data which has been obtained is an important topic for scientific due diligence audits. The following sections will provide guidance on the best approach to assess the preclinical study program, with a particular focus on:

- General aspects of assessing data
- Toxicology
- Pharmacology
- Deciding whether to progress to clinical studies

Assessing the data

Preclinical studies will produce a large amount of data, often too much to be easily interpreted during a due diligence investigation. The following sections cover the 'general' checks which you should make prior to delving into the specific details.

Is the study package complete?

There will be a number of different preclinical studies performed for any new drug. Depending on the stage of development they may be already completed, in planning, or in progress. It is therefore important to keep an overview of the studies to ensure that all of the necessary reports are available. You should ask for and be provided with a list of the preclinical studies by the company being investigated. If possible cross-check this information with that in the **investigators brochure**, a compiled summary of the information available for an investigational drug.

Information on potential competitors (and thus alternative approaches to the study) may be found in the Drugs@FDA database. This includes links to the **summary review** (sometimes known as the **summary basis of approval** (SBA), a document summarising the information evaluated during the drug approval process). The SBA provides a quick overview of the most important information and can help you determine where other companies have used similar approaches in their preclinical trials. This is particularly important when using animal models of disease, regulatory authorities will often raise similar objections regarding the models' suitability and so can help you plan your development strategy.

Which studies will need to be performed? In general you will want to see the following:

- Safety pharmacology studies
- Repeat dose toxicology studies
- Toxicokinetic studies
- Pharmacokinetic studies
- Reproductive toxicity studies
- Genotoxicity studies
- Assessment of carcinogenicity (most commonly required for drugs intended for long-term treatment or those with particular cause for concern).

Regulatory authorities make exceptions for drugs which are highly 'necessary', i.e. ones which target life-threatening or serious diseases for which there is currently no good treatment. An example of this might include a highly effective drug for HIV or some types of cancer – in these cases the delay required to do these tests will lead to patient deaths. If an exception is granted then the toxicology and related studies may be shortened significantly, based on the pragmatic (if depressing) logic that the patients will die *anyway,* even if the drug is toxic.

If you do have access to the investigators brochure, you should check to see that all of the studies which were performed are included in the document. If some have been left out then you should determine *why* this has occurred. Was it considered to be irrelevant? Are updates to the study in preparation? Is someone trying to hide unfavourable data?

Do the studies make sense?

It doesn't help if the required studies have been performed yet the data generated was rubbish. For this reason the *results* of the preclinical studies should also be checked. The aim of this assessment is to determine if the studies were performed correctly, if the data was analysed correctly, and whether anything has been left out or overlooked.

You should examine the design of the preclinical studies. Remember that these tests are intended to provide data which will allow an estimate of the *human* response to the drug. Thus the data should be examined with an eye towards eventual clinical trials. Is the route of administration similar or equivalent to that used for the human pharmaceutical? Is the animal model being chosen *relevant*, in that is appropriately represents human physiology or a human-specific response to the drug being used? Were sufficient animals used to provide a statistically relevant read-out of the attribute being tested? How did the researchers determine the appropriate sample size and can you follow their reasoning?

If the study has been completed and the report is available, then you should look at the results obtained. Do the findings make sense, given what you already know about the mechanism of action? Or are there odd and unexplained results? Do the results allow you to extrapolate to human dosages? Do they provide you with information you could take into clinical trials?

The work should also have been performed correctly and with a sufficiently high standard. Did the group perform their work under Good Laboratory Practice (GLP) conditions, or in accordance with ICH guidance requirements? Many companies, particularly smaller biotech firms, will have a sightly haphazard approach to pre-clinical trials which may lead to problems later in the approval process. Check that the studies match the generally-accepted approaches.

Another area to focus on is the quality of the drug being tested. Is the test sample a pure sample of the active ingredient, or do the tests involve a formulation representative of the final drug product? If a pure active ingredient is used, is it pure *enough* to avoid off-target effects from degradation products or other contaminants?

Are the analytical methods valid?

Before you can assess the pharmacokinetics and pharmacodynamics of a drug, you need a way to *detect* that drug. More challengingly, it must be detected within a fluid such as blood – a complex mixture of biological molecules which can easily hide the drug of interest. Thus all detection methods involve a method of separating the various components of the mixture from one another.

Small molecule drugs are usually assessed by classical separation methods such as high-performance liquid chromatography (HPLC), liquid chromatography/mass spectrometry (LS-MS) or capillary electrophoresis. Biological drugs are significantly larger and more complex which can lead to challenges with chromatography-based methods – many laboratories will instead use antibody-based immunoassays or bioassays specific for the mode of action.

Regardless of the method used, it is important that it has been *validated*, formally tested and shown to be suitable for use. It is a general assumption from all regulatory bodies that any analytical method or equipment has been thoroughly validated to ensure that it will consistently provide the correct results. A *lack* of validation is a Very Bad Thing indeed, one which will quickly lead to an audit finding and often product recalls.

As part of the due diligence process, you should check that the analytical methods in place are appropriate to detect the drug being used. Do they work for your specific drug? Are they industry standards, and have they previously been used for other drugs? Do you have access to the validation reports? Did the method pass validation? Or are the methods in use pharmacopeia methods which do not require formal validation testing?

Toxicology

Every pharmaceutical is toxic, eventually, and even the safest of drugs can kill a patient if they take enough of it. The problem for those developing drugs is not to determine *whether* a drug is toxic (because they all are), it is to determine *at what concentration* it becomes toxic. In the ideal world this concentration will be a long way from the treatment concentration. In many cases, unfortunately, it is not. This makes it vital to accurately identify potential safety hazards of any new drug before it is tested in humans.

The non-clinical studies make up a major part of the toxicology data needed. They are particularly important when identifying upper limits for dosing, the point at which the drug is expected to have an unacceptably toxic effect on the patient. This limit will be tested in Phase I trials with steadily-increasing dosages, but the trial designers must know where the limit is. Thus the animal work will let you estimate how toxic your new drug is, allowing you to enter clinical trials at a far safer dose.

When looking at a series of toxicology studies, the first question which should be asked is whether they are even relevant. This seems like a no-brainer, but biological therapeutics in particular are known to have (a) very specific targets and (b) species-specific immune reactions to biomolecules. A mouse may happily tolerate an injection that will lead to massive and potentially deadly immune responses in a human. Is the chosen animal model one which would react to the drug in a similar fashion to a human patient? Has it previously been used to check similar drugs? Do the models in use match with the typical regulatory requirements of two separate animal models? Regardless of what was used, can you justify the decision from a scientific basis in response to the inevitable health authority questions?

The question of relevance also extends beyond the animal model to the conditions in place during the studies. The material which was used during animal trials should be comparable to the material which will be used during clinical trials – there should be no changes in excipients or concentrations occurring. Similarly, is the tested dosing regimen (and route of administration) relatable to the clinical trials? This is not as important for lethal dosage testing but many drugs will require long-term toxicity assessments. These will need to match the length of intended treatment, e.g. a treatment intended to be taken for many years must be shown to be safe in long-term animal treatment studies.

Assuming the studies were relevant, the next thing to check is the actual results. What drug concentration led to toxic effects, both in single dosing and long-term? When did the animals start to die? This value is usually provided as the LD_{50}, the dosing rate at which 50% of the treated animals will die, but you may see other values given. What was the highest dose at which *no* toxic effect was seen? This is known as the NOAEL (no observable adverse event level) and it is a very important number for calculating your clinical dosing level.

If toxicity was observed (which will inevitably be the case) then you should have access to long, boring tables detailing exactly toxic responses were observed. These are often categorised by severity, you should keep a close eye on those considered to be serious or critical. Some toxic effects may

disappear following the cessation of treatment (these are usually considered reversible), some will remain as a sign of irreversible damage. Do some toxic symptoms occur more commonly during repeat-dosing studies? This could indicate a cumulative toxic effect for the drug, something which will need to be followed up in later studies.

The study program should have identified which organs were most affected by the drug treatment. Does this correlate with the bio-distribution of the drug determined during the pharmacology studies? If you compare your drug to similar drugs (those within the same chemical class, for example), are they 'expected' toxic effects? Can you match the toxic effects observed to the drug itself or the drug metabolites? If the latter, then which enzymatic pathways are responsible for creating this toxic metabolite? Do the development team have a plan in place for reducing formation of these metabolites, perhaps via co-treatment with a second medication?

You should check if there is a linear dose-effect relationship – i.e. if you give the drug at several concentrations, do the therapeutic effects and observed toxicity also vary in a linear fashion? Linear relationships are generally preferred as they make for more reliable calculations of toxicity in both humans and animal models.

The final goal of all these extensively-documented studies is to decide how to perform the upcoming clinical trials. This means that, by the end of the toxicology study programme, the company should be able to say that the planned treatment dose and duration is safe for humans. More importantly, they should be able to say this and *then support the statement* with data. If your assessment shows a mismatch between preclinical results and the planned clinical trials, this is a red flag that definitely needs further investigation.

Pharmacology

Pharmacology is the study of how drugs work, a field which is usually divided into pharmacodynamics (what the drug does to the person) and pharmacokinetics (what the person does to the drug). The primary pharmacology of a drug is essentially *how it works* – how the drug affects its target molecule, what the mode of action is, what activity it has after this. The secondary pharmacology covers off-target effects, the unwanted actions of the drug on other, non-related systems. All of this is, unsurprisingly, a complex field and one which requires the investigation of a number of different areas.

Animal studies provide an initial look at the pharmacokinetics of the drug in question – looking at how the drug is processed by the body before, during, and after the time when it exerts its medical effect. This is particularly important when determining **ADME** rates (Adsorption, Distribution, Metabolism, Excretion) – essentially the rates at which a drug is taken up by the body, passed around, turned into other chemicals, and then dumped out by the kidneys. From a drug development point of view, the main parameters which need to be determined are the drug half-life (the time required for the concentration or amount of drug in the body to be reduced by half), dose-response (the relationship between the amount of drug and the physiological effect), and drug-drug interactions (the way in which your drug interacts with other drugs). All of these lead into the determination of drug safety and so are required for determining the dosages which will be used for the first clinical trials.

The ADME assessments should help you determine the time in which the drug will be actively circulating within the body – i.e. the time in which it can actually do what it is meant to do. This is usually the point where you need to do a 'sanity check' against the planned approach. For example, if the drug is intended to be given, say, twice a day, will the circulation time actually match that dosing regimen? Alternatively, what if the drug is slow to clear from the body? Does this mean that the long treatment series which has been planned may lead to a toxic build-up over time? It is very common to modify the treatment approach based on results from early preclinical trials, thus performing this kind of basic check is important for long-term success.

One important factor to check during due diligence is whether the animal model in use was suitable. Is the particular biological system which the drug targets comparable between the animal model and in human patients? What differences could exist between the species? How might they affect the studies? Do similar metabolic pathways exist in both species, allowing you to estimate safety?

When the study was performed, was it possible to ensure that the drug reached the target organ in the correct concentration? This is sometimes different due to species-specific transport or metabolic pathways. If the drug was administered in a manner which could inhibit uptake, how was this possibility controlled for? The classical example here is the addition of a drug to animal feed, in which digestive processes may strongly affect degradation and uptake. The scientists who developed the non-clinical trials should have commented on this as part of their study reports.

Progressing to clinical studies

The non-clinical studies act as a natural check-point, the point at which the pharmaceutical firm must determine if their chosen approach is the right one. It is easy to develop a drug is effective in cell culture, it is significantly harder to make it work in a living being. Getting to this point will require a number of decisions, choices regarding the composition of the final drug, the route of administration, the proposed doses, etc. By the end of the non-clinical program each of these decisions should be well-supported by data from targeted studies. As part of due diligence you should investigate why these decisions were made and whether they can be supported by the data at hand.

For example, suppose one route of administration has been chosen for the drug. *Why* was this particular route chosen? Does it match with the requirements of the drug or the patient population? For example, a complex device for injecting your drug won't work if your patients are all self-medicating children. Which other options could have been taken for administration? Would they perhaps be a better approach?

Based on the data generated, you should be able to follow the processes involved in transferring the drug around the animal body. How does the bio-distribution of the drug look? Does it tend to accumulate in some tissues, is it rapidly cleared by the kidneys, does it accumulate in a lump within the arteries? (This last one is not a good sign). This information should be available both in qualitative forms (i.e. where in the body is it going?) but also qualitative (what concentration or absolute amount of drug is reaching each tissue?).

You also need to determine which enzymes are involved in modifying or metabolising the drug. As these are the underlying mechanism by which your drug is modified or degraded, they play a vital role in determining the final ADME kinetics. One complexity which sometimes causes problems here is the differential expression of proteins within different tissues – a drug may be processed via one pathway in the liver and another in the heart, for example. This requires you to look at bio-distribution from a molecular perspective – do the different protein profiles present in each tissue or organ play differing roles in the effect of the drug?

The excretion and clearance of your drug from the body is an important factor in safety and dosing. Sick patients will often have problems with drug clearance – you may be treating people with impaired kidney or liver function, for example. If this is the case, has a safety factor been built into the clearance calculations? How was it determined? Is it supported by scientific data and standard approaches?

The information provided by these preclinical studies should be merged with available scientific knowledge. Is the molecule or class of molecule being developed one which is *known* to have toxic effects – or even likely to be, based on the structural features? Compare this candidate to other drugs on the market and other candidates at the company. What are the advantages and disadvantages of each? If the drug appears to be less effective than ones already on the market, then it is unlikely that

the drug will be worth taking through clinical trials. An equivalent or better drug, by contrast, has a good chance to carve out a section of the market for itself.

If the molecule being investigated is still at the preclinical trial stage, you should ask if the data available so far would suggest that it will be safe in human trials. Or are there likely to be toxicity issues that will need to be dealt with? If so, how is the company planning to deal mitigate these issues? Are there open questions which will require further experiments or studies? What will these cost in terms of money and time?

The final goal of all this work is to decide whether the benefits of the new drug outweigh the risks involved in taking it through clinical trials. The benefits and risks apply both to the company (as failed drugs are very expensive) and to the patients (as failed drugs can kill people if they are unlucky). From a financial point of view the decision to progress a candidate molecule to clinical trials is a factor of the total potential market, the comparison to other products on the market, and the likelihood that the candidate will be non-toxic and effective. From a patient-safety point of view, the decision comes down to the level of safety demonstrated in the preclinical studies. In both cases it is a matter of weighing the risk/benefit ratios. This is never a clear-cut decision and it inevitably revolves around the severity of the disease being treated, a risky drug may be worth pursuing when it treats fatal cancer but not when it reduces symptoms from the common cold.

Despite this the decision to progress is rarely a decision for the person performing scientific due diligence. You will examine data, identify gaps and further studies to be performed, note indications which may be profitable niches and make recommendations. The final decision, however, will be made at an upper management level. Your job is to allow your managers or clients to make this decision with as much foreknowledge as possible.

Chapter 8. Clinical trials

Clinical trials are the ultimate test of whether a drug is suitable for its use as a human pharmaceutical. A prospective drug must pass a number of clinical trials prior to approval. Many, many drugs will fail at this point, usually due to a lack of efficacy or unexpected safety problems. This risk of failure should always be taken into account when examining new technologies for investment.

The importance of clinical trials leads to a huge amount of pressure to succeed – this pressure means that many companies will look for any possible way to spin the results in their favour. Tricky statistics, recast outcomes, and subgroup analyses will pop up almost everywhere, inevitably making the drug seem better than it actually is. Those performing scientific due diligence will need to be even more careful than at other stages.

Clinical trials are divided into **Phases**, ranging from Phase I through to Phase IV, with each subsequent phase being larger and more expensive than the previous one.

Phase I trials are safety trials, most often conducted using healthy volunteers and designed to identify side effects associated with the drug. Every drug has unwanted effects, Phase I trials are necessary to determine what they are and whether they are dangerous. The trials also study **ADME** (absorption, distribution, metabolism, and excretion) – how the drug is taken up by the body, shuttled around from organ to organ, broken down into other compounds, and gotten rid of. This information is combined with ascending dose studies, in which the dosage of therapeutic is slowly increased over time to determine the point at which safety concerns occur, to determine what the most likely therapeutic dosage should be in later work. The majority of small biotech firms will have a compound or two in Phase I trials.

Phase II trials begin to focus on efficacy, taking place in patients rather than the healthy volunteers of Phase I. The numbers involved are small, usually less than a few hundred, and will often involve multiple **treatment arms** in which patients are given different dosing regimens to see which is the most effective. Phase II is usually too small to definitively state whether a drug is beneficial or not, but it provides the scientific data which the later studies will build from. Successfully passing Phase II will provide the first major boost to a biotech start-up and is usually the trigger for another round of investment by larger firms (this is often agreed upon in the licensing or investment terms).

Phase III is much larger, involving hundreds to thousands of patients spread across many different medical centres. The trial size provides an excellent overview of potential safety issues, in particular long-term or rare effects, and so are carefully examined by regulatory authorities. The size and duration of these studies comes with a correspondingly high price tag which ensures that Phase III trials are reserved for a pharmaceutical company's best prospects. Phase III compounds will nonetheless often fail to meet the defined **clinical endpoint**, disappearing in a short flurry of newspaper articles. Medicines developed for several different indications will need to run a Phase III trial for each – with a correspondingly high price tag.

Lastly there are **Phase IV** clinical trials, which occur *after* the pharmaceutical has received approval. Phase IV trials answer remaining questions about efficacy or safety and thus usually involve large numbers of patients over a long period of time. These trials are often required for drugs which have been approved via an accelerated regulatory pathway to demonstrate that there are no underlying safety issues which have been overlooked.

The following sections will provide guidance on the assessment of clinical trial information during due diligence.

Initial assessments of clinical trials

Although later sections will cover the specifics of individual clinical trial phases, there are many common factors which should be taken into account. This section will therefore cover the general, factors relevant for any clinical trial being examined within a due diligence investigation. These include:

- Obtaining the required information
- Determining completeness of the data package
- Basic clinical trials requirements
- Study design and outcomes

Obtaining the required information

The first step is to obtain the information you need for assessment. The company being investigated will, naturally, have the most details regarding their own trials, however this kind of information is treated as highly confidential. You will normally only have access to the reports while on-site or via secure virtual data room. Although the specifics will vary with the situation, you should attempt to obtain the following documents as a starting point:

- Detailed descriptions of ongoing clinical trials, including the timelines, recruitment rates, budgets, and meetings with health authorities.
- Clinical study reports of completed clinical trials
- Extracts from relevant dossier modules, if written
- Copies of any existing marketing authorisation licences
- Copies of recent periodic safety update reports or serious adverse event reports (particularly if they were 'expedited' due to severity)
- Copies of internal safety summaries
- Copies of institutional review board approvals

The aim is to determine if the ongoing trials are being correctly performed, that the trials are assessing the correct endpoints, that the work is being performed in a high-quality way, producing reliable data, and has sufficient oversight from the sponsoring firm. It is often helpful to have a physician with expertise in the disease area on the assessment team to help determine if anything is missing. Safety problems should be brought to the attention of the team as soon as possible, above all any serious adverse events or frequently recurring adverse events. This is particularly important for new chemical entities or a new method of delivery.

Although most of your information will come from the company under investigation, you should be aware that these documents may be biased in favour of their product. Thus to ensure balance, you should try to obtain as much information from external, third-party sources as possible. Overviews of relevant clinical trials may be found in the published literature or online databases such as ClinicalTrials.gov. These do have their limitations, however. Although obtaining details of *planned* trials is easy, obtaining *results* is more difficult – details will rarely be uploaded to ClinicalTrials.gov and even scientific papers will normally only have heavily aggregated information. This means that specific information is difficult to find and you will often be dependent on whichever details can be scraped together.

Is the study package complete?

As with the preclinical study package, keeping track of the various clinical studies involved in a development program can be difficult. As before, you should request a list of the preclinical studies being performed by the company being investigated. A thorough overview may also be found in the **investigators brochure**, a listing of the currently available information designed for clinical investigators. If you do have access to the investigators brochure, you should check to see that all of the studies which were performed are included in the document. If some have been left out then you should determine *why* this has occurred. Was it considered to be irrelevant? Are updates to the study in preparation? Is someone trying to hide unfavourable data?

Documentation and planning of clinical trials is incredibly important, with one of the most useful documents being the clinical trial protocol. This document which describes how a clinical trial will be conducted with details such as the objectives, design, methodology, statistical considerations and organization of a clinical trial. The document should essentially lay out all of the processes which will be performed in the course of the study.

When performing due diligence, you will want to look at the protocol of any study which has been finished, is being planned or is currently underway. It is important that the design, statistical power, and endpoints of the study are sufficient to show the hoped-for outcomes. In other words, do the chosen endpoints make sense given the disease and therapeutic? Does your trial contain enough people to even detect any therapeutic effect which may occur? We'll go into more detail on this in the following section on statistical power.

Are paediatric populations addressed?

Many countries are now requiring that drugs also be developed for paediatric (i.e. child) patients prior to or directly following approval – this is, for example, a requirement for new drugs in the EU. These regulations are considered a simple way to ensure that the drug is available for the smaller (and thus less profitable) paediatric population. You should check the status of paediatric clinical trials during the course of due diligence. Has a new formulation or dosage been developed for the market? Has the relevant study already been performed? Is it planned?

If aiming to submit in the EU, has the **paediatric investigation plan** (PIP) been submitted and agreed upon with EMA? The PIP is intended to ensure that sufficient studies are performed to allow approval of a drug for children, the details of this can be discussed with EMA as necessary. Some drugs may not need paediatric formulations. The medicine may be exempt (when it is not safe for children) or given a deferral (when data from adults needs to be gathered first). You should determine the current status of the PIP (in preparation, in discussion with EMA, agreed upon, waived or deferred) to determine what further work is required.

Have the basic requirements been met?

There are a few basic requirements which need to be met by any clinical trial. If there is only limited time for the assessment, it should at least be ensured that the following requirements have been checked for all clinical trials which are in scope:

Good Clinical Practice and Auditing

As mentioned, there are a few basic requirements which any clinical study should be able to meet. The most obvious of these is that it should be conducted according to **Good Clinical Practice** (GCP), a set of guidelines covering the correct way to run and document a clinical trial. These are many-faceted, but pay particular attention to documentation, to informed consent, and to quality control to ensure that the results obtained are scientifically useful.

Another basic is the requirement for an independent check of the trial documentation and results by a quality assurance group. This is often not done for every single clinical trial but should certainly be completed for every major or pivotal trial performed. This will, naturally enough, be documented and

you should in turn get access to a copy of this report during due diligence. Check the kind and number of audits which have been performed. Were there any findings associated with the audit? Were there recurring findings (i.e. signs that a problem keeps coming up). If there were findings, then were they adequately addressed and do you have a documented response which describes how they will prevent it from occurring again?

Ethics approval

Another basic thing to check is whether the clinical trial has permission to be run at all. Health authorities require the filing of an abbreviated dossier before granting approval for human trials to begin (e.g. the US IND) – if this permission hasn't been granted then you have some serious problems to explain. This is not the only permission required. An ethics sign-off on the trial design, performed by the **Institutional Review Board**, is also needed – this is necessary to show that the trial is being conducted in an ethical and non-evil way.

Are you working according to guidance?

Health authorities often publish **guidance documents**, documents which describe the 'ideal' way to go about doing something, be it developing a new drug or cleaning the manufacturing floor. There are, naturally enough, guidance documents associated with clinical trials – these usually cover the safety and clinical requirements for any particular trial. Some guidance documents are specific to certain drug classes or therapeutics, you may for example find guidance which is specific for the development of new vaccines or genetically-modified patient cells.

Always check to see if a guidance document specific to your drug is present. If yes, has the company followed the recommendations of the document? If not, what are the gaps? If no specific guidance is present, check that the general recommendations of the broader guidance documents have been followed.

The Case Report Form

You should also have access to samples of the **Case Report Form** (CRF), a questionnaire used in clinical trials to collect data from the enrolled patients. The CRF should be able to capture all data which is generated for a patient over the course of the study – this includes adverse events and data from post-study follow-up visits. CRFs are unfortunately notorious for having errors in them, usually due to hurried data entry or mistakes moving data into electronic formats. As such, it is important that a CRF is audited, a process in which the data is checked (automatically or manually) and strange or nonsensical entries flagged as *queries* for a second check. Only once these queries have been resolved will the data be used in the final clinical trial report. As resolving queries can be a very expensive undertaking, you should check to ensure that the company has a process in place to minimise the impact of human and machine error – either at the initial data gathering stage or during quality assurance checks.

Is the CRO reliable?

Very few companies run their own clinical trials these days, small biotech firms in particular will almost never have the resources available. The work is usually passed on to a **Clinical Research Organisation** (CRO), a company which specialises in performing clinical studies. These companies have strong contacts with hospitals and experience in the specialised area of trials, thus CROs are able to get the work done at a lower cost and with less problems than a pharma company would when trying to do everything themselves.

In theory, at least. As with everything, some companies are good, others are bad. Some provide well-documented results and cleanly-organised files, others mismanage the studies and lose vital documents. You should check the reputation of the CRO as part of your due diligence – are they well regarded? Or not? A bad reputation usually means difficulties for your company as you attempt to track their work and results in the following months or years – in some cases this may even push back approval timelines.

Clinical study design

There are many ways to design a clinical trial and many different factors which need to be balanced against each other. The exact approach taken will assess the patient population, the expected response to treatment, the required statistical power, biases inherent to different trial types, and available trial locations. All of this sounds complex and indeed it is – study design is a field in which many different specialities need to work together to achieve their goal. As such this section will not go into the details of study design lest this book rapidly be taken over by a new theme.

The important question to be asked during due diligence, in concert with a clinical trial expert, is whether this study was designed in a way which will achieve the intended goal. If this can be answered with a 'yes', then there is a good basis to proceed.

Randomised controlled trials

Randomised controlled trials (RCTs) are the gold standard in the clinical study world. Participants in the clinical trial are randomly assigned to one of the treatment arms – placebo, investigational drug, current treatment, etc. RCTs control all factors except the identity of the treatment and thus are the closest that clinical trials can come to a laboratory experiment. As such they also provide the most useful clinical data for use in regulatory applications and thus are ubiquitous in Phase II/III trial design.

Most RCTs will either be parallel-group (in which participants are assigned to a treatment arm for the duration of the trial) or crossover (in which they switch from one treatment to another). Cross-over study designs are more common amongst generic and biosimilar manufacturers as a way to show interchangeability of their products. Determine what approach is used in the clinical study being examined. Does the study design make sense? How are patients being allocated to their groups? Are the comparator treatment arms sensible or are they being designed to make the investigational drug look good?

Blinding is the act of preventing the participant from knowing which treatment arm they are in. This is usually single-blinded (the patient does not know) or double-blinded (neither the patient nor the physician know). Blinding is not always possible (e.g. if patient participation in a certain program is required), however blinding will provide more convincing data. A lack of blinding is not normally a problem but justification should be available, as such you should check if blinding is present in the trial, and if not, what the reasoning for this is.

Statistical power

Statistical power is, formally defined, the ability of a statistical test to reject the null hypothesis (e.g. 'there is no difference between these treatments') when an alternative hypothesis (e.g. 'treatment X is better') is true. More commonly, if perhaps not perfectly accurately, it is used as a description for the sensitivity of a clinical trial – i.e. whether it is capable of detecting a clinical effect from the drug being tested.

Statistical power is related to several factors. This includes:

- The size of the population being examined. Small statistical effects are easier to detect in large groups and thus the easiest way to improve statistical power is to enrol more patients in your clinical trial. This is, however, an expensive process and adds to the already-impressive costs of a study.
- The magnitude of the effect being measured. If the effect is easy to detect or there is an obvious difference between the potential outcomes, then the statistical power will be higher. For example, it will be easier to detect clinical efficacy when the outcomes are 'completely cured' or 'dead' compared to one which involves a three-month extension of survival.

- The significance criterion. This is formally a measure of the likelihood that an effect will be observed when no effect actually exists. Essentially this is the limit which is placed on the data to decide when clinical efficacy is considered to be 'real'.

Although many people will have a grounding in statistics, assessment of statistical power in planned clinical trials is a difficult and involved task requiring significant experience in the field. This task will therefore normally be performed by specialist consultants during the due diligence process.

Endpoints

The clinical endpoint of a trial is the parameter which is being measured as a marker of the therapeutics' success. A trial will normally have several of these, most important of which are primary endpoints. Primary endpoints are the main parameters being assessed, the trial will be designed to have sufficient statistical power to detect changes in these endpoints. Secondary endpoints are those which are informative for the study but which are not the primary focus – these will usually be examined via post-hoc analysis of data once gathered.

There are many different endpoints which are possible in clinical trials. From a patients' point of view, the most relevant endpoints usually relate to survival (overall survival, progression-free survival, or disease-free survival) or disease symptoms (such as time to relapse or severity of symptoms). Trials with good results in these endpoints will be highly convincing to investors and regulatory authorities, and usually have few problems with approval. These endpoints are, however, more challenging ones in which to observe a significant effect – a fact which in turn raises the size and thus cost of the clinical trial.

It is perfectly possible to use time to progression or prolongation of survival as an endpoint for your clinical trial, though these are comparatively imprecise measures of efficacy. Even an untreated group will show significant variation in survival over time, comparing between groups to find statistical significance thus becomes very difficult. A trial of this type also cannot use the easier (and cheaper) option of comparing to historical data sets (data from studies conducted in the past). Instead, you will need the additional statistical power provided by randomly assigning patients to your drug or a comparator.

To avoid the uncertainty and cost of survival-related endpoints many studies will use surrogate endpoints, a biomarker which correlates to a clinical endpoint and is intended to act as a substitute. The classical example here is blood cholesterol levels, which act as a surrogate endpoint for heart disease. The problem with this approach is that *correlation is not proof* of a clinical benefit – relying on correlation alone makes the whole package harder to get through the approval process. When dealing with surrogate endpoints, check carefully what the rationale for these endpoints are. Is it a scientifically justifiable link? Have they been used by other trials? Does it strongly correlate to clinical outcomes?

Anti-cancer therapeutics

Cancer holds a slightly special place in the world of drug approvals and clinical trials, as the word 'cancer' often obscures the fact that there are a vast number of *types* of cancer. The identity of the initial cancerous cell will strongly affect the final outcome – the disease progression from a white blood cell to lymphoma is very different to that of the neuron to a glioma. Different therapeutics are necessary for each form and thus any new 'anti-cancer' drug will only be approved to treat a small subset of the potential cancer types. This leads to a lot of competition in 'common' cancer indications while rarer forms will often be essentially ignored.

Cancer therapeutics also tend to be more toxic than their counterparts in other indications. Indeed the toxicity of a drug may mean that it is not acceptable for initial treatment but instead only be approved for second- or third-line therapy – i.e. only once the previous drugs have failed. In general, however,

toxicity is more tolerated in cancer therapeutics by regulators. This is due to the simple fact that the usual alternative (dying of untreated cancer) is worse than any side effect could be.

Clinical trials are often challenging. Patients enrolling are usually those who have already tried the normal first or second-line drugs, they are inevitably very sick and often not expected to survive for long. A cure is the ideal result for the new drug but this is sadly not often the case – many times a new drug will only be able to increase survival time rather than prevent death. It is thus difficult to estimate what the true benefit of a drug is – will it really be possible to get marketing approval on a drug which extends survival by a few months? If so, will any insurance company actually pay for it? Or is the minor extension in survival actually a significant breakthrough which is merely being masked by the poor prognoses of the patients in the clinical trial?

This complexity makes life difficult for pharmaceutical companies, health authorities, and the due diligence investigators. As a rule of thumb, speed to market is the most important factor in success. This means that the company may target the most promising indication for their drug, even if it is a rare form of cancer, and then attempt to expand the approved indications at a later stage. Is this being attempted? If so, do other, more efficient, ways to reach the market exist?

Country-specific requirements

Different countries will have different requirements for a clinical trial. The health authority of Japan, for example, requests that at least one clinical trial be performed using Japanese citizens to ensure that no race-specific differences in efficacy or safety exist. The US and EU may require that bridging studies be performed using material specific to the local market. You may even be asked to investigate different indications or clinical endpoints.

Because of this uncertainty it is vital that the company be in contact with health authorities *before* designing and running trials. Both the FDA and EMA allow meetings between an applicant company and health authority experts, these are an excellent opportunity to receive feedback on the choice of trial design, comparator treatment, endpoints, and the required level of efficacy to be considered a 'success'. In your role as due diligence investigator, you should have access to records of these meetings. From these you can determine what was discussed and which suggestions were made by the authority. If suggestions were made, were they then implemented by the company? Did the health authority have a favourable opinion of the clinical study program, and did they consider that it would be sufficient for the regulatory filing?

Clinical trial results

Once complete, a study will be 'wrapped up' with a final Clinical Trial Report, a document which provides a comprehensive overview of all the gathered data. You should be able to examine the Clinical Trial Report for all studies which have been completed. In some cases the report may still be in preparation (they do take a very long time to write, after all), in which case you should at least have access to the statistical analyses.

Studies which are still running are more difficult to assess. In particular you will often be told that data is not available as the study is still **blinded** (i.e. knowledge of which patient gets which treatment have not yet been released). It is nonetheless often possible to obtain information on adverse events in *all* treatment arms. Although you will not know which events are associated with the drug, you will be able to get an overview of potential safety issues. It is also possible to compare the enrolment data to compare against the planned intake. This lets you determine what fraction of the clinical trial has already been completed and thus roughly how long it will take to complete the entire study.

Safety and Adverse Events

One of the major factors being assessed during clinical trials is that of drug safety. Regulatory authorities place a heavy emphasis on drug safety, a natural outcome of the many, many occasions in which untested or uncontrolled drugs have led to patient deaths. Safety information is thus extremely

important for your scientific due diligence – a drug which fails the safety requirements will not be approved and thus will not make a profit for the licensing company.

Adverse events, the unwanted effects associated with taking a drug, are the most important way to observe safety problems during clinical studies. The importance of adverse events cannot be overstated. They are a fundamental way to indicate potential toxicity problems, they will be combed over during the dossier review process, they will even be listed in the paper insert included with the drug packaging. Adverse events in clinical trials are thus a critical area to examine during scientific due diligence.

Make sure you get *all* of the available information from the company being investigated – be as persistent and irritating as necessary. The investigators brochure is a good place to start, it should contain all of the adverse events detected in clinical trials so far. Cross-check this information against other sources – adverse events which have been reported but then left out of the investigators brochure are a major red flag and often indicate that someone is trying to hide an unflattering safety problem.

Once you have obtained the listing of adverse events then it is time to assess their criticality. In general this work should *always* be performed in concert with an expert in clinical drug safety as interpreting adverse events is a difficult field, one in which you definitely need expert advice. Support from the experts involved in assessing the preclinical work is also quite useful, many of the more critical adverse events can often be linked to observations during animal trials.

You should also cross-check the adverse events which were observed against those reported for similar drugs – in particular those of the same molecular type or targeting the same indication. This information is freely provided by health authorities for approved medications and so is usually straightforward to compare. In general a lower rate or severity of adverse events is a plus for the drug under investigation, however you should never exclude a drug from consideration purely because of equivalent or slightly increased adverse event numbers.

Phase I Clinical Trials

A clinical trial program begins with Phase I trials, small studies with a handful of healthy volunteers. Phase I trials are safety trials, the aim is to determine whether the drug in question is safe for further tests in larger numbers of people. More specifically, the researchers aim to determine the **safety profile** of the drug, in particular the **dose-limiting toxicity** which the drug causes on the various organs of the body. Phase I trials will thus involve many tests and assays which are related to patient health and potential drug toxicity – measurements relating to potential efficacy are usually an afterthought.

As part of developing the safety profile, the study will attempt to determine a maximum tolerated dose (the highest dose which can be safely administered) and a minimum effective dose (the lowest dose which provides an effect). These points will help to anchor a safe dose range, the dosing used for later trials will then be chosen from within this range.

Pharmacokinetic studies are a major part of Phase I trials, the aim is to develop data which will support the previously performed animal studies. This means that scientists will look at drug distribution within the body, the kinetics of the various ADME pathways, the half-life of the drug in the body, whether any drug-to-drug interactions occur, and whether different dosing regimens will affect the overall efficacy of the drug. It is important to define which differences exist between the animal models and human patients – for this reason you should expect a lot of comparative statistics and mathematical modelling.

Typical due diligence questions

The similarity between Phase I and early pre-clinical work means that many of the questions you need to ask are the same. The can roughly be divided into those affecting the set-up, those affecting the results, and those affecting extrapolation of the results.

First comes the set-up of the study. Were the correct analytical techniques and assays used? Do they match with the measurements that were performed to show safety? Are the assays validated ones? Were the study participants a homogenous group (i.e. 8 white men, which is easier for statistical analysis) or heterogeneous (10 men and women of varying races, which is more representative)? Was any extra effort put into testing people with potential variation in clinical responses – such as children, immunocompromised patients, or those with long-term illnesses? Were any of these people part of the target population?

Next we look at the study results. What sort of blood and serum levels of drug were observed? What were the kinetics? Does the drug tend to hang around in the body following dosing or is it quickly cleared? How variable are these results from patient to patient? Consistent ADME kinetics make for a reliable drug even in disparate patient groups – which in turn makes it easier to get market approval. An important question to ask is whether the kinetics determined in preclinical trials match up with those found in the Phase I trial – can they be considered predictive, or is there a major difference? If so, why?

Last you should look at factors which will affect your ability to extrapolate from these initial volunteers into the wider group of patients. If people of differing genders, ethnicity, or ages were part of the trial, can you see any differences in drug kinetics or potential safety? Several studies have shown that some adverse events are more common amongst particular ethnic groups than others, making this an important question for long term drug safety. Were any of the potentially variable responders mentioned previously in the group, and if so, were there any differences observed? Was there any mention of drug-drug interactions? Given all of this information, is it likely that you will need to perform further work to clear up variability in special population groups or in certain cases of co-medication? These can be requested by health authorities during the approval process and can make for an unexpectedly expensive surprise.

Dose selection and progression to Phase II

The aim of every researcher performing a Phase I trial is to gain enough data to support a Phase II study. This is the point where you really begin to see if the drug works as hoped or if it is merely an expensive mistake. However the success of a Phase II is built upon a well-performed Phase I, in particular regarding the development of the target dosage and administration schedule.

Phase I involves testing steadily-increasing levels of drug. Based on these results the clinicians should now have a good idea of what the optimal treatment regimen for real patients would be. This includes the target dosage (how much drug is given), the administration schedule (how often the drug is provided), and even confirmation of the route of administration (how the drug is given). These parameters will then be used as the basis for testing in Phase II.

Although Phase I focuses on safety rather than efficacy, it is possible to get a few hints as to whether the drug will work even at this early stage. If nothing else the study should demonstrate biological activity of the drug on the target system. Ideally the drug will have a clear mode of action with easily detectable **surrogate endpoints** (measurable parameters which are related to but not directly equivalent to the therapeutic action). By checking these endpoints in the initial safety trial it is possible to see if the drug is acting in an expected manner and thus whether clinical proof of concept will be achievable, i.e. it helps demonstrate that the therapeutic will have practical use later down the line.

Making this determination is a difficult decision. The majority of compounds will progress through Phase I trials, currently available animal models of toxicity are quite reliable and so it is rare to be completely surprised by new adverse events. Assessing a successful Phase I trial is thus a tricky problem when performing scientific due diligence – many drugs will look promising at this stage but then fail during Phase II when efficacy becomes much more important. For this reason it is very important to cross-check with the development and preclinical efficacy data, this maximises the chances of avoiding an expensive failure in the next stage.

Phase II clinical trials

Phase I trials determine safety whereas Phase II trials determine *efficacy* – i.e. whether the drug actually does what it should do. Efficacy can be thought of as a combination of two factors: biological activity (whether the drug acts on its target *in vivo*) and clinical proof (whether the drug has therapeutic activity). What you actually consider to be *proof* of efficacy is something which varies depending on the drug being investigated.

For example, an anticancer therapeutic may lead to slower tumour growth or reduction in tumour size. These are great things to see but are only preliminary signs of efficacy because your ultimate goal is to *cure* the cancer – this is a final proof of efficacy. However if you are developing a drug for patients who are already very sick then removal of symptoms may be a perfectly valid final goal for efficacy. You can get a drug to market based on preliminary signs of efficacy alone but it is significantly harder to get insurance companies to pay for it.

An important factor for any due diligence is to nail down the definition of efficacy being used in the clinical study being investigated. The definition will vary from clinical trial to clinical trial and so it is important to know what it is in your particular case. More importantly, this should be very clearly written down *before* the clinical trial starts – changing the success conditions after starting the trial is a sadly common way of reworking an otherwise failing trial. A typical example of this would be performing excessive subgroup analysis and then stating that, although the trial was overall a failure, the drug was highly successful in white women between the ages of 40-45. All of the reports and marketing material will then focus on this subgroup. Subgroup analysis can have its advantages but is very often used for statistical trickery, thus the due diligence investigator should be alert for problems.

Study design

Phase II is the point in the development process where things start getting very expensive. An appropriately-powered study will require a significant number of patients, which in turn leads to significant costs. As a result there is significant pressure to get the 'right' results – i.e. a successful outcome for the drug being tested. Many drugs will 'fail' in Phase II trials, they will not be brought forward into Phase III. This is most commonly due to lack of efficacy but also often occurs due to strategic considerations – the company does not feel that this drug suits their current focus. These out-of-focus drugs are common choices for an out-licensing approach and so will regularly turn up during due diligence investigations.

A major goal of Phase II trials is to make the final decision on dosing and treatment schedules, with some trials testing several different dosing regimens to determine the most effective format. This is essentially the last chance to do so, Phase III trials are intended to be conducted according to the 'final' therapeutic setup. Phase II trials are also conducted in 'normal' hospitals with real patients, unlike the healthy volunteers of Phase I. The trial tends to act as a practice run for the eventual 'real' use in the clinic, complete with all the minor problems and annoyances this involves. If practical problems with the distribution and administration of the drug are going to occur then they will usually show up at this point. Try to ensure that the participating clinicians and researchers keep track of these problems, as they will be vital for fine-tuning your final market-ready drug.

It is possible to use a number of Phase II trials to target different possible indications for your newly developed drug, the aim being to see which areas your drug is most effective in before targeting that

as the first indication for obtaining market authorisation. This 'clinical trial screening' approach is expensive and so usually only performed by large pharmaceutical companies. It does, however, allow for the fastest possible route to market – this makes it very important for potential blockbuster drugs with multiple targeted indications. Despite this clinical assessment should focus on the target indication for which the drug is being developed. Expansion to new indications is a good bonus to the license but should be considered secondary as the initial approval will provide the basis for all following work.

Study results

The most important information to come out of a Phase II trial is that of clinical efficacy. As mentioned previously, the definition and expectations for efficacy can vary based on the drug and disease in question. The question for you, in your due diligence role, is simple: can you state, based on the data gathered and the definition of efficacy, that clinical efficacy has been shown?

There is more to it than that, of course. Does the data available indicate that the compound is likely to be superior to other comparators, either with respect to safety or efficacy? Or will you have to rely on demonstrating **non-inferiority** (i.e. your drug is no better and no worse than others). Based on this, what is the likely size required for a Phase III trial to conclusively demonstrate superiority or non-inferiority? What sort of risks are possible when you move into Phase III?

Phase III clinical trials

Phase III trials are the 'big' trials, involving hundreds to thousands of patients in the attempt to comprehensively show clinical efficacy. Millions of dollars will be spent running these trials, failure at this stage will send shareholders running for the exits. Success, however, means a strong chance of marketing approval and thus finally being able to make a profit from the drug.

As a general rule you will need to have shown clinical efficacy in two independent clinical trials before you can obtain marketing authorisation. Approval may sometimes be granted based on only one trial, but you need to have some pretty damn amazing results. Ideally the trials will be **randomised clinical trials**, in which patients are randomly assigned into one of the trial treatment arms – preferably double-blinded in that neither the patient nor the clinician knows what treatment they are receiving. This is generally considered the gold standard of clinical trial design and thus is the most likely to gain regulatory approval.

Planning

There are several controversial discussions that will happen during trial planning. One of these is the choice of clinical endpoints, and the second is the selection of the comparator treatment.

The choice of endpoints affects how you can declare the trial a success – some endpoints may be easy to achieve, but are pointless in the real world, others are difficult but extremely persuasive. In general the most widely accepted endpoints are prolongation of survival (e.g. for cancer therapeutics), prevention of a life-threatening event (e.g. medicine against heart attacks), or relief from symptoms (e.g. pain-killers). You will also see improved drug safety as an endpoint in cases where there are several drugs already available to treat the disease. **Surrogate endpoints** are sometimes accepted in rare diseases but gaining acceptance will be significantly harder.

As part of due diligence, you should examine the endpoints which have been selected for the clinical trial. Do they make sense given the disease indication? Are they likely to be met during the trial, based on the results from previous phases? Are they 'real world' endpoints such as prolongation of survival rather than abstract surrogates such as changes in biomarker levels?

The selection of comparator treatment acts to determine your competition – the drug that you need to beat for success. In general, Phase III trials will be run as a *comparison* between the new drug and the current state-of-the-art treatment. Very few clinical trials still compare the tested drug to a placebo as

this is considered essentially useless information (no-one cares if your drug is better than nothing, it needs to be better than the current options). A common alternative is to have one arm of the clinical trial use the current 'best practice' drug, while the other will use a combination of this drug and the new drug under investigation. In this way patients are guaranteed to be treated with something that works and may additionally experience a benefit from the new drug. This approach is usually followed in oncology trials, where it is considered highly unethical to not provide the correct treatment to potentially dying patients.

As with previous stages, the pharmaceutical company can enter into discussion with the health authorities regarding the best approach to take. In general this will include the major issues (comparator, endpoints), as well as more technical questions such as the time-points of interim analysis and the type of statistical testing in place. As mentioned previously, you should always attempt to get copies of the meeting minutes – were the suggestions from the authorities followed? If not, why not?

Clinical trial results

The final outcome of the Phase III trial will have a major effect on your chances for gaining marketing approval. This makes the results from the trials a vital area to focus on during scientific due diligence. Assuming that the appropriate endpoints were chosen, your first question should be to determine if they have been achieved. How does the data look? Is there a difference between the comparators or treatment arms? If so, is it both statistically and clinically significant? Is it a relevant result, given what you know about the disease? Is it convincing for the authorities?

You also need to look at the results in the context of other therapeutics. Are there other drugs which are in development for your chosen indication? Your drug may be better than the chosen comparator, but is it likely to be better than those soon to enter the market? Next check that the regulatory requirements for clinical trials been fulfilled. If there were suggestions or requirements from authorities during pre-trial meetings, have these been addressed?

The most important outcome from Phase III is the demonstration of clinical efficacy. If this has been shown then the likelihood of regulatory approval is high, which in turn means that the originating company is unlikely to license the technology without some hefty repayments. Be on the lookout for post-hoc demonstrations of efficacy or unwarranted subgroup analysis. In other words, if the company is focusing their claims of success on a smaller sub-group of the trial participants (e.g. Asian women over 50) rather than the entire participant population, then you are probably looking at statistical trickery. This approach may be justified in some circumstances but it requires a solid basis of underlying science to explain why this subgroup is more relevant than any other one.

Chapter 9. Marketing

All pharmaceutical companies are, at heart, aiming to make money. They do this by selling the drugs which they have painstakingly nurtured through the development process – sales which have to make up for the vast expenditures prior to this point. Yet pharmaceuticals are similar to every other business, people will not buy the product if they are not convinced of its effectiveness. This is where marketing comes in.

As with every other product in the world, pharmaceuticals are marketed to customers. Unlike many other products, there are a number of regulations which cover just how pharmaceuticals can be marketed – designed to prevent unscrupulous practices or patients being taken advantage of. Thus as a rule the target customers for pharmaceutical marketing are health care professionals rather than patients themselves. Pharmaceuticals can be marketed in a number of ways, this may include free samples such as trial packs of medication, labelled notepads, stress-balls, USB keys, etc., it may also include sponsoring continuing medical education seminars. Marketing will also be involved in the production of scientific articles, online videos, social events for physicians, and trade show exhibitions.

Marketing and the financial group will be involved from the early stages of drug development, as a company will only decide to pursue a drug if the financial factors line up. In other words the market size and potential market share must support the development expenses, while the proposed product needs to be equivalent or better than the current competition. The marketing group will use market research and knowledge of the drug to put together a strategy for marketing and sales. This strategy will help provide goalposts for the final drug to meet, for example, recommending that a particular route of administration or pack size be targeted to maximise uptake by patients.

The marketing group will also be involved in determining the nomenclature of the drug. The **International Non-proprietary Name** (INN) provides a scientific name for the active compound which is trademark-agnostic – it will also be used by other manufacturers of the molecule. The **trade name** is specific to the product being manufactured and will be the most common name which patients come into contact with. Choosing the best trade name can be a long and arduous process. Marketing will help to find catchy names, legal will help check if they are safe to use, regulatory will help persuade the health authorities that the name is sufficiently distinct from other drugs to avoid problems with patients – eventually a final decision will be reached. Although this seems like an obvious step, you should check that the INN and trademark are in place and that they have been accepted by the health authorities. Many drugs have required a last-minute change in name due to authority objections – don't let this happen to you.

Competitor analysis

No drug is released onto an empty market, there are always other options available for patients to use (this applies even if the other options are not very good). Thus it is very important to know the competitive landscape of the drug you are investigating, comprising the other drugs which may act as competition to yours.

Currently available drugs

The first step is to identify *currently available* therapies for the disease which you are targeting. These should be assessed to determine their 'fit' – the degree to which they actually meet the medical requirements. Where do they have limitations? Where are they particularly strong? What sort of sales are they pulling in? Can you estimate the profits resulting from these sales, given what you know of their likely manufacturing and marketing spending?

Sites such as ClinicalTrials.gov are excellent here, as they contain many details about currently-running or recruiting clinical trials. This is a legal requirement in the US, which means that the site

entries will include details such as enrolment criteria, treatment arms, and clinical endpoints. Based on the entries you can often gain an idea of studies being conducted, the timing of their results being released (and thus their eventual entry to the market), and the timing of critical transitions such as Phase I – Phase II. The patient population being examined will also help indicate what the eventual labelling will target, e.g. first line or second line therapy.

Upcoming drugs

The next stage is to determine *upcoming* therapies – technology which is being developed with the intent of treating your target disease. This can be very difficult to determine when competitors are in early development, normally you will first begin to see press releases when prospective drugs reach the clinical trial phase. Efforts should be made, however, as it helps your company prepare for the inevitable upcoming competition. These can affect your plans in different ways, even without considering the effect on eventual market share. The upcoming therapy may become a standard treatment, at which point you will need to consider it as a potential comparator during clinical trials (particularly problematic when there was no existing treatment beforehand). If you are targeting a relatively rare disease then two separate clinical trials for different drugs may exhaust the potential pool of trial participants, delaying study time-lines significantly.

Online and literature searches will help gain an idea of potential competition, as most novel drugs coming into development will be announced in a journal article first (particularly those spun out of academic research). Early-stage candidate chemicals will be described in biochemistry journals, clinical studies in medical ones, etc. There are, however, several disadvantages to literature searches. Many competition products will not be mentioned in journals, particularly those entering the big-pharma pipeline. The peer-review process ensures that publication will lag behind the actual studies, you may find that a paper is published several years after the work it references, at which point the company may be well into clinical development. There are also many, many potentially-relevant publications every year – important information can be difficult to find amongst the rubbish, while accessing these journals can be very expensive if you do not have an institutional subscription.

Beyond online searches, conferences focusing on the disease in question are also an excellent source of information on upcoming clinical trials. Many researchers or start-ups will present initial results as poster presentations, which will often be found online or available in the conference proceedings. Posters will only provide limited data and rarely include detailed information on safety or efficacy. However the pooled results or choice of analysis can tell you how the trial has progressed – for example, a significant amount of post-hoc statistical testing usually indicates problems with the original endpoints.

Identification of differentiators

Once the product profile has been determined it should be compared to your ‘ideal’ drug. What improvements would be required to take a significant market share from this competition? What would make a notable difference for marketing purposes – think of alternative routes of administration or stronger dosages for improved patient treatment, different formulations for reduced side-effects, etc. These critical improvements will be best determined by the marketing experts and consulting key opinion leaders in the therapeutic field.

The competition should be assessed to identify ‘differentiators’, factors which would push a patient, a doctor or a payer to choose one product over another. More specifically, you are looking for differentiators which make the technology you are investigating a better choice than those currently on the market. For example, an improved safety profile or longer-lasting effect is a significant bonus for patients and thus will improve sales of the eventual product. As a rule of thumb crowded markets (with multiple products targeting the same indication) will place greater importance on small differentiators than empty ones – thus even if the product being examined is not *that* much better than the competition, it may be enough to gain market share.

The quickest way to identify differentiators is by comparing the labelling information which is provided in the **package insert** or **summary of product characteristics** (SmPC). These documents conveniently package the most important information on each product together in one freely-available place, including safety and efficacy results, treatment regimens, and product formulations.

This comparison should focus on areas which have the greatest potential market appeal. These are often factors such as how many times the treatment needs to be performed per day, how it is prepared, how much it costs patients, whether the drug can be taken at home, etc. The comparison is most useful for markets with multiple competing products – this provides you with the greatest amount of information. New drugs will be working in a comparatively empty space and so will need to work with correspondingly higher uncertainty.

At this point it is worth checking potential differentiators in the 'real world' by asking the opinion of experts in the field.

Interviews with experts

Doctors normally have their own opinions on whether a drug is effective and safe. The collective opinion of all doctors in the field is the major force driving sales, market share and overall success for any particular drug. As such one of the best ways to identify the product parameters which may influence a physician's opinion is to simply ask them. Thus the face-to-face interview.

Interviews are a great way to dig out details on opinions and follow up on potentially interesting topics identified during the discussion. The downside is that they are expensive – even a 'normal' physician will require a consultation fee for their time, payer representatives or **key opinion leaders** (who tend to be more connected and influential) require even more. This also requires time to perform the interviews and collate the unstructured data to create a useful overview. A faster, cheaper process involves sending surveys to a larger group of experts. This removes much of the flexibility of interviews, but lets you quickly check a broad base of opinions.

Regardless of the method, it is important to avoid projecting the bias of the interviewer onto the subjects. For this reason it is usually better to outsource the process to a neutral third party.

Potential market share

The ability of a drug to make the company a profit is based on the size of the market, the share of the market it can take, and the amount of money the drug can be sold for. This estimate will normally be done by the commercial assessment group and so is outside the scope of this book, but a few basic comments are included here.

A good first step here is to check epidemiology databases (such as that of the CDC) for the disease prevalence and thus potential patient population. Compilations of data by commercial firms will help you to identify the size of the market, i.e. the sales for a product or product class. This is generally provided as a market report containing comparisons to similar products or typical benchmarks for the indication. Market sizes for novel products or rare disease therapeutics are more difficult to determine as there are no exact comparisons for the drug being developed. The usual approach here is to compare to other drugs in the same indication or in fields with a similar market dynamic – this at least provides some information for the assessment.

Next determine the potential market size. This is an art to itself, but as a rough guide you will need to work from the patient population (based on disease incidence), estimate if the population will be increased through marketing, and determine if there are upward or downward trends in the overall population. Very small market sizes are normally a sign that orphan drug designation is required to obtain a reasonable return on investments.

Revenue will be based on a number of factors and becomes increasingly complex as you begin dealing with more markets. This is generally a topic for marketing, finance, and market access experts

and so rarely falls under the scientific due diligence side of the equation. However the rough approach would be to look at the prices currently charged for equivalent or similar therapies, the reference pricing provided by government bodies for drugs of that class, and the level of competition from other drugs. The end result will be an expected revenue level and this will then be compared to the costs and risks involved in getting the drug to market. This in turn helps you decide if the investment is worthwhile.

Reimbursement

The other side of marketing is market access, which can be thought of as the negotiations required before someone (the government, companies) will actually *pay* for the pharmaceutical. These groups are, sensibly enough, collectively known as **payers**. Patients rarely pay for the entire cost of medication themselves, instead using public or private health insurance to spread the risks and costs over a large number of people. The company or government department offering this insurance determines the price which they will pay for the medication – this will come down to a number of factors including efficacy of the treatment, prevalence of the disease, and how serious the disease is.

It should be determined at an early stage how the drug will be reimbursed, in particular whether the indication being targeted is covered by health insurance reimbursement plans. Orphan diseases or highly-expensive treatments may not be covered due to a lack of cost-effectiveness, this can severely limit the profitability of the drug being developed. Bulk-billing systems such as the US Medicare/Medicaid may also limit the type of medication which they are willing to pay for.

Planning for reimbursement is made more complex by countries with a large number of competing insurance providers such as the USA – in these cases market access is dependent on the outcome of negotiation with payers and other organisations. As payers will often have further questions regarding the drug, this effectively adds a second layer of regulatory approval which must be solved prior to reaching the market.

Cost-effectiveness is also a vital parameter for gaining market acceptance. A drug may be perfectly effective at curing a disease, but if it costs millions of dollars to do so then no-one will pay for it – the business of health care is still, despite what many may hope, a business. This fact is the basis of pharmaco-economics, a field which concerns itself with the economic evaluation of drugs. This involves a comparison of the costs associated with the drug (i.e. how much you need to pay for it) versus the benefits (efficacy, quality of life, etc.).

The difficulty here lies in comparing the severity of different diseases and thus the benefit associated with treating it. As an example, which is the more severe of these options, and which has the greatest impact on healthcare spending: late-onset Alzheimer's disease, Down's syndrome, or complete blindness? A difficult decision, isn't it? To attempt to resolve these comparison problems, a generalised measure known as the **quality-adjusted life-year** (QALY) was developed. In this system a year of perfect health is considered to be 1 QALY and a year of being dead is 0, with various levels of disability in-between. Although the process of mapping 'health' to 'fractions-of-a-QALY' can be contentious the QALY approach is generally very useful for comparing dissimilar drugs or treatments. In particular QALY calculations allow those who *pay* for the medication to calculate whether the benefit it brings is worth the cost – as an example the UK has previously described a cost-effective medical intervention as being one costing less than GBP 20,000 per QALY. This number then becomes the basis for negotiations between the pharmaceutical company and the payer, negotiations which will theoretically lead to an acceptable price.

Pharmaco-economic comparisons have become widespread in the pharmaceutical world, particularly when dealing with smaller countries that may not have the healthcare budget to buy every new drug coming onto the market. As such, pharmaceutical companies need to be proactive with performing their own studies in order to show the (no doubt exceptional) cost-benefit ratios for the new drug. What does this mean for you and your scientific due diligence? First, you should ensure that there is a

plan in place for obtaining reimbursement in whichever region you are targeting. You should at least ensure that there is a plan in place, that there are no obvious risks involved, and that a cost-benefit analysis has been performed in favour of using your drug.

Chapter 10. Intellectual property

Pharmaceutical development is built on knowledge and innovation, the intellectual property of scientists and companies. This means that *protecting* this intellectual property is vital for long-term success – no-one will continue making profits when their bright new ideas are stolen by others. Indeed most drugs will lose up to approximately 90% of their market share once patent protection lapses and generics enter the market. This is a particularly large problem for small-molecule drugs, which are relatively simple to 'copy' in generic form. Biologicals are much harder to manufacture and so it usually takes more investment to make a biosimilar copy – this in turn preserves a greater fraction of the originator's market share for the first few years.

There are two main approaches used to defend intellectual property, that of **patenting** and that of **data protection**. Regulatory exclusivity has a similar effect to patenting in providing market exclusivity, but has its own requirements and difficulties. Patent protection is by far the most powerful of these options, but companies will use any method available to protect their market share. The following sections will cover the various approaches available.

Patents

Patents are vital for protecting intellectual property, they allow you to essentially lock other groups out of using your idea for a set period of time. The typical patent lasts for 20 years and during that time only the inventor or those they license the rights to are able to use the invention commercially. In exchange, the idea becomes public information after this period of time – free for use by anyone. It can take several years for a patent to be approved after the application is filed, this is known as the 'patent pending' period.

The strength of any particular patent comes from the coverage it provides, the remaining lifetime of the patent, and the ability of the patent to block third parties from using similar approaches. For this reason patent assessments will require extensive checks of prior art, potential challenges, and similar patents belonging to other firms.

The difficulty with a typical pharmaceutical patent is that the clinical trial process will take up a large chunk of the available time, often up to ten years. This means that a pharma company will have less time to make a profit from that innovation when compared to other high-technology fields. There will be immense pressure to make a massive profit during the few years where the product is patent-protected and on the market, a timeline which may be further shortened through successful patent challenges from competitors or generic manufacturers.

The fact that pharmaceutical patents have this reduced profit-making period compared to other branches makes them less-tempting for investors. To offset this, and thus improve investment in new drugs, both the EU and US offer 'extension' programs. The European Supplementary Protection Certificate (SPC) comes into effect for products with market approval after the original patent expires, it adds 5 years protection to make a maximum time-on-the-market of 15 years. This can be extended by another 6 months if data is on paediatric patients is provided by the company. The US equivalent is known as a patent term restoration, it also adds 5 years to the patent protection but has a maximum protected market time of 14 years. Paediatric data can be used to increase the data protection time (more detail in the following section) but do not affect the patent limit.

All of this seems clear enough. In reality, patents turn into a minefield of complexity the moment you enter the real world. Almost all pharmaceutical companies will register multiple patents covering their active ingredient, the combination with excipients, special packaging, etc. This **patent thicket** allows the drug to be protected from other companies for much longer than the usual period of time. It also has a nasty habit of catching even large companies out – you may suddenly discover after several years that you are unknowingly infringing on another's patent. For this reason a firm will *always* want

to involve a specialised firm in the patent assessment, although everyone involved in due diligence should at least understand the basics of patenting. Every patent with commercial importance will be challenged at some stage and so this knowledge helps everyone assess the upcoming risks.

Patent attorneys and other IP specialists perform a number of vital actions. They check for other patents which may impact on your intellectual property, identifying those which may be problematic and indicating when those patents are expected to expire. As drug companies operate in a global market, this will involve checks in multiple regions – at a minimum in the US and EU. The regulations covering patenting also differ from country to country, with many different interpretations of patentability existing. These differences may affect or even prevent product launch in some countries.

An intellectual property due diligence is a long and involved process which will require gathering a lot of background information. It will focus on assessing four things

- The scope of coverage
- The validity and enforceability of the patents
- The freedom to operate
- The ownership of rights.

Scope of patent claims

A patent contains a number of **claims**, statements which cover the circumstances or uses which are under the patent protection. These claims will range from highly specific ones detailing the exact intended use of the drug through to very broad ones which attempt to cover as many uses as possible.

Patents in the pharmaceutical world are usually those for composition of matter (CoM) or method of use (MoU). Composition of matter patents cover unique ingredients or the use of old ingredients in a novel way, method of use covers the method used to treat the disease, including different drug regiments or treatment combinations. The patent will be issued for an invention which is *useful* (not a waste of time), *novel* (never described before) and *non-obvious* (it would not be instantly thought of by a typical expert in the area). Of course patents are sometimes issued for rubbish claims, but these tend to fall apart very quickly when challenged in court.

Assessment will review the patents held by the company, their claims, and the history of prosecution (challenges through the courts). Almost all patents with a commercial application will eventually be challenged in court, the question is whether the patent is strong enough to hold up to this challenge. The type of claim affects the level of protection – composition of matter patents are comparatively wide-reaching, whereas method of use patents can often be circumvented by changes in the treatment regimen or targeted indication.

It is also important to remember that just because a patent claim *exists* does not mean that it is *final.* Court challenges may lead to some claims being disallowed or modified and so a balance must be struck in the claims which will be made. Broad claims will provide a wide layer of protection against competitors, but narrow and specific claims will be more likely to stand up to challenges in court. Although broad claims are helpful, you should be able to identify at least one narrow claim concerning the product – this will be the cornerstone of any court defence.

Validity and enforceability

A patent is useless if it cannot be defended in court, with one of the worst outcomes of any patent challenge being a court order to strike down the patent. To prevent this scenario the investigating team will need to carefully check that the patents involved cannot be rendered invalid or unenforceable.

Invalidation of patents

A patent may be *invalidated* for several different reasons. The most common of these is the existence of **prior art** such as publications or journal articles. If an idea was disclosed to the public *prior* to being patented then the idea is no longer considered 'novel' and thus cannot be patented. This also applies to publication of an idea which is *similar enough* to that of the patent to make it an 'obvious' discovery. To avoid this patent-killing problem, all patent attorneys will do extensive searches of the prior art to ensure that no such publications exist. This is never 100% possible, of course, as even descriptions in other countries in other languages can be considered prior art – the level of certainty depends on the amount of time (and attorney fees) which can be invested.

Other reasons for invalidation also exist – including prior use of the method, double-patenting of the invention, failing to adequately describe the invention, or having derived one invention from another patent. These invalidation grounds will not be brought up by the patent office themselves (as they have enough to do), but rather will be conclusions drawn in the course of patent litigation.

Unenforceable patents

A patent may be considered *unenforceable* in cases where the submission process has not been correctly followed. This includes situations where the applicant has known of prior art or data which does not support the invention, but then failed to disclose it during the submission. The investigating patent attorney will review the patents as well as related filings and declarations to see if any discrepancies exist.

Freedom to operate

Freedom to operate is a term which indicates that the manufacture, use and sale of your product will not impinge on patents from other companies or individuals. This is particularly important in fields such as pharmaceuticals which rely on novel products, techniques and methods. As part of a patent assessment, the patent attorney involved in due diligence will provide the reassurance that the approach is 'safe' – development is ok to proceed without being threatened by patents currently in existence. This assessment of freedom to operate will be provided for multiple areas, including the drug in question, the treatment process, the delivery method, and even the manufacturing technique. In practice this check involves exhausting searching of registered patents to find those which could, possibly, maybe, be relevant.

It is often the case that a blocking patent will appear – one which prevents you from following your original process. It is sometimes possible to attempt a "design around", a redesign so as to avoid this blocking patent. A manufacturing process may, for example, have several new steps added to avoid a single patented method. Alternatively a licensing agreement may be entered into with the owner of the blocking patent, or a challenge may be brought in the court or patent office.

Ownership of rights

It seems like a basic thing to worry about, but the patent assessment will also verify that the licensor company actually holds the rights to the patents in question. This will be performed by checking assignment records at the patent office and viewing copies of all licensing agreements. Although basic this is an important part of the due diligence process and should never be skipped – even if the company assures you that everything is fine. *Especially* when the company assures you that everything is fine – despite confident claims a surprising number of start-ups forget to correctly transfer IP from their scientist founders to the company itself.

Initial due diligence

The intellectual property assessment will usually be performed by a corporate attorney and patent attorney, supported by experts as needed. These experts do not come cheap and so a two-step process is used to minimise costs. An preliminary screen of patents will be performed towards the end of the due diligence process, when the chances of the deal going ahead are highest (larger deals will begin earlier due to the complexity of the IP situation). Then a full patent investigation will be performed

once the terms of the license have been arranged, immediately prior to the signing of the contract. This provides a way to find IP issues early on while still avoiding major costs for investments that are doomed to failure. It should be noted that different firms will place different levels of importance on patent investigation – generics manufacturers, for example, will spend large amounts of money determining the exact boundaries of the patent protection prior to entering the field.

Part of the initial screen will involve examining 'open' patent information, those which are available outside of patent databases. This may include listings on sites such as the **FDA Orange Book** or other sources. Basic patent details may also be provided by the licensing firm themselves as a way to kick-start the investigation process. A high-level search for prior art and potential blocking patents will be performed during the initial screen, review of information obtained from open sources will also be done.

Intellectual property attorneys will usually be familiar enough with the field to provide further advice, such as describing the strengths of the patent and the ways in which it could be extended to block generic competition. This may include line extensions, new formulations, or sneaky additions to the labelling information of the originator drug. The attorney should also be able to identify the likely timing of generic entry to the field. Other experts may be called in to provide specific information on areas of interest. For example, a CMC expert may be asked to provide an opinion on the protection available for manufacturing processes – they can indicate which steps may be easily worked around and thus how well-defended the process is.

Data protection

The other form of intellectual property protection is known as data protection or data exclusivity, it is a way to slow down competing firms who are developing generic versions of the original product. The origins of this approach lie in the regulatory pathways used by manufacturers of generic medicines. To prevent unnecessary duplication of animal and human trials, generic manufacturers may *refer* to data generated by the original innovator company (i.e. they can include reference to this data in their regulatory filings). In this manner they can show that their generic drug is effective and safe without the need to run a large number of highly-expensive clinical studies.

However, this can only be done after a defined period of time. In the EU, for example, a generic manufacturer may only refer to this data after the data exclusivity period of 8 years – in other words the *data* of a new innovator product is protected for 8 years after marketing approval. The generic itself cannot be approved and sold in the EU before 10 years of market protection is finished, this can be extended by another year if further indications are authorised for the drug within those first 8 years.

New drugs which have been registered as orphan drugs, those which treat a very small patient population, have a *market exclusivity* period of 10 years. This is a higher level of protection than data protection as it completely blocks similar drugs for the same indication from being brought to market – here 'similar' is defined as having a similar main molecular structure and mode of action. The market exclusivity period can be further extended by another 2 years if the required paediatric patient data is provided to EMA.

A similar approach is possible in the US, albeit with shorter data protection periods. The data protection lasts for four years after approving the initial product, the market protection for five years. Market protection can be extended by three years for a new indication, data exclusivity by half a year with paediatric data. As in the EU an orphan drug designation brings an extended period of protection, however in the US this extended protection only lasts for 7 years.

Assessing the intellectual property

Both patent periods and data exclusivity should be considered when investigating a potential licensing opportunity. The exact coverage of the available patents should be summarised, including their claims, the regions in which patents are valid, and how long the patents will last. It is also important

to check what data or planned studies are available which may help obtain extended patent or data protection.

One area which is often overlooked is the exact composition of the transferred IP. Many times a company will have sub-licensed technology from other companies for their development or manufacturing, (platform or enabling technology is a typical example here). This will usually not be part of any transfer deal, (the technology is not theirs to transfer, after all) and so will require a separate deal with the original licensor. Keep in mind that this may also apply to clinical data if the study was performed by a university or private researcher rather than the company itself.

As the patent work will (and should) be outsourced, your role in due diligence will usually be limited to checking the reports from the patent lawyers. The reports will be long, but there are two main questions you should be able to answer: How strong is the patent protection for the drug? How long will the patent protection last? These two factors allow you to protect your intellectual property, which in turn allows you to turn a profit from the newly developed drug. This, in combination with the opinion on freedom to operate, lets you estimate your strength of the market position.

Chapter 11. Concluding the investigation and making recommendations

At this point the team will have gathered all of the relevant data, checked reams of documents, and gone through the potential risks and benefits in excruciating detail. All of this information will be brought together into a final report which will provide the conclusions and recommendations of the team. Before this happens, there are a few 'final questions' regarding the overall potential of the technology which should be answered.

Revenue and 'fit'

No-one buys or licenses new technology for fun, so the most important question is whether it will make a sufficient return on investment for the acquiring company. All predictions are prone to error, naturally, but there are some factors which give a good indication of the likelihood of success, including the total size of the market, the ability to penetrate that market, and the 'fit' of the technology to the company.

- Do you know the revenue potential of the new technology? In other words, how much money is it expected to make?
- What is the size of the total addressable market?
- What is the possibility of penetrating that market? E.g. the tenth drug in a crowded market will find it harder to gain market share than a new and exciting one for an as-yet untreatable disease.
- Can you estimate the products' gross margin (the difference between the selling price and the cost to produce) and operating margins (the return on sales)?
- Does the drug fit what you are currently doing? In other words, will it help improve sales or distribution of your other products, or will you somehow cannibalise your own profits?
- Is the *size* of the deal correct? Will it be providing a revenue stream that is close to your current revenue, or is it far larger or smaller? Tiny revenue streams are often not worth your time, large ones can be too much for a mid-sized company to handle.
- This also applies when investigating so-called **enabling technologies**, ones such as slow-release capsules which improve your current products. If you are investigating one of these, how will the technology add to your current revenues, and how long will it take before you can do so?
- If it is specific to a certain geographical area, does that work with your company's current location or will you need to build up a new marketing and sales division?
- Do you have a sales group with sufficient reach and motivation to market this drug in the defined area?
- Are the expected revenues consistent with our current company size?

Differentiating factors

Being able to make a return is heavily dependent on the effectiveness of the drug – a drug with a significant improvement in efficacy over the current market will sell far better than that improvement would suggest. In other words, markets tend to function according to 80:20 principles, the majority of the sales will go to the minority of the products. This makes your differentiating factors of critical importance to eventual success.

Differentiating factors should have been assessed during the due diligence process and thus you will have a list of competitor products for these indications, their formulations and dosages, advantages and disadvantages, and approval status. As part of the assessment, identify the most common problems or limitations with the current options.

- What are the unmet medical needs which still exist?
- How do these match up with the advantages of the drug under investigation?
- Can you identify key factors which will cause this drug to be successful?

Future-proofing and further development

Longevity is important to the overall success of a pharmaceutical. The typical drug will have approximately a decade to earn revenue prior to entry of generics into the market. This long timespan means that future and upcoming technologies are just as important as those currently available. The most useful part of a due diligence report is often the prediction of the future – the information about which products are currently in development and which will be on sale within the next 4-6 years.

- Do you feel that you have gathered enough information regarding competitor products?
- Are you confident that no other products will come onto the market next year and blow your plans out of the water?

Just as important are the future implications of your own technology and the ways in which it can be developed to create further revenue streams.

- Is the technology something which can be used for other therapeutic indications or in other fields?
- If yes, what are they?
- What will that do to your planned revenue and market size?
- Will this deal actually cover all of these potential uses, or have they already been licensed out to other companies?

Manufacturing

Manufacturing of the drug product is a very important part of your development process and eventual commercial success. The complexity of this manufacture depends on the drug in question, biological drugs are significantly more complicated than small molecule drugs, but command correspondingly higher revenues. It is therefore important to determine if the manufacturing process is within your firm's level of competence – i.e. whether it can be dealt with in-house or whether significant help from consultants is required.

- Is the current manufacturing process suitable for your company?
- Who will make the drug?
- Will your company need to manufacture it in their own facilities, via a contract manufacturer, or through the original licensors' facilities?
- Do the necessary contracts already exist or will you need to approach other companies to determine costs and availability?
- Will technology transfers between sites be involved, with their extra associated costs and validation requirements?

Intellectual property

Intellectual property underlies the entire idea of licensing technology – you cannot license what does not belong to you, after all. This means you have to be very certain of the IP situation before making the final recommendations.

- Have you checked the status of the key patents in all the major countries?
- Do you have freedom to operate in both the manufacture and sale of the drug?
- Are you certain that the licensing company actually has the exclusive rights to the technology they want to sell or license to you?
- Are there competing or overlapping patents which will lead to a nasty patent dispute several years down the line?

Regulatory affairs

Regulatory approval is required to sell and thus make a profit from any drug you license. The progression through the approval process and the quality of the regulatory dossier thus play a very important role in the investment decision.

From a due diligence point of view, a product which has been approved for marketing by the FDA or EMA is much more trustworthy than one which is still in development. The approval process and associated authority questions act as a due diligence investigation, one performed by a very picky and experienced team of investigators. As a general rule, if the FDA or EMA have accepted the new drug then you can rely on the overall quality of the underlying science.

- If a product is on the market, is it being manufactured correctly and under GMP?
- Is it being marketed in accordance with the approved dossier?
- Is the dossier up to current standards?
- Are the required post-approval regulatory processes (e.g. safety updates, adverse event reporting), being followed?
- Were the clinical trials set up correctly? Run correctly? Was the data gathered correctly? Does the methodology make sense?
- Are the clinical study sample sizes, treatments arms, dosages, chosen endpoints and the like sufficient to support approval?
- Do the timelines and costs make sense?

Final recommendations

Once the investigation is complete it is time to determine the final recommendations and write the concluding report. This is done by assessing the risks and opportunities, seeing how the two relate to each other, and determining if the results are on average positive. No drug development program will be perfectly good, very few are perfectly bad. Instead you will need to deal with the complicated mixture of both which so often characterises scientific work.

The recommendation will combine assessments by experts from regulatory, CMC, clinical, preclinical, legal and marketing. These will focus on the scientific and commercial risks and benefits associated with the technology. Investigations of smaller biotech companies will also look into the company itself, not just the technology. Each expert is likely to have created a list of risks and potential problems by the end of the assessment process. It is expected that they will rank these in

order of importance and consequence, after which it will be combined with assessments from the other experts to create a final list of potential problems. This in turn will help guide the final decision.

Specific evaluations should be made as to how convincing the information available is – and perhaps more importantly, what gaps remain. A slightly higher burden falls on the regulatory expert at this point, as they will need to assess whether the information available can support a filing for marketing authorisation. Some firms may place the regulatory expert as the overall co-ordinator of the scientific due diligence process for this very reason.

A final report containing all assessments and an overall recommendation should be prepared once all the sub-groups have made their conclusions. This final report should be written in a way which is understandable by non-experts – more specifically, it should be understandable by senior management. Management will make the final decision on investing and thus need a clearly-stated and easily-understandable document to work from.

At minimum, the report should contain the following points:

- A summary of findings from each expert
- A highlighted list of the key risks, their impact (potential delay in submission, further studies required), and the likelihood of them occurring.
- Recommendations as to whether the project is worthwhile (the Go/No-Go recommendation) and an up- and downside to each possible option.

Chapter 12: Appendix I - So you are being audited

Small biotech companies will often look to sell or license their technology and intellectual property to a larger company. This allows them to focus on their strengths (new and exciting drug ideas) while taking advantage of the big pharma strengths (late-stage development and marketing). When this happens they will be on the opposite side of the due diligence process – an equally stressful place to be in.

Suppose you are working for a company which is aiming to license their technology out. What should you do to prepare for the upcoming scientific due diligence inspection?

Plan ahead

You should be planning for the eventual acquisition from the very early stages of your company development program. Leaving everything until the week before a horde of lawyers and experts turn up is basically a recipe for failure – so be smart and plan ahead!

You should be documenting everything in the development program from the beginning – this includes experimental protocols, results and reports. Ideally this documentation will be done in English – although biotech companies come from all around the world, the main language of investment and business (and thus of due diligence investigations) remains English.

The timing of the due diligence can vary, but will normally occur at around the same time as signing of the **term sheet**, the listing of financing and legal requirements for the proposed investment. In some cases the due diligence will occur as a final check prior to signing the agreement, in others it will occur directly afterwards. Regardless of the timing, you should be ready for the due diligence process.

Know your technology

If you are aiming to license your technology, then you should *understand* your technology. You should be very familiar with the data generated so far and be able to explain what it implies for the overall project. This includes both the overall implications and the smaller ones – all deviations should be explainable and their lack of effect on the quality of your technology clear to see.

Understanding doesn't stop at your office door either – you should also be able to comment on competitors and how their technology compares to your own. This does not only apply to *current* competition but also those which may arise in the next few years. The auditing group will certainly be investigating this themselves and so you should be prepared with your own assessment.

If there are potential issues, then you need to know the impact this will have on your idea and your business. Ideally, you will have a plan in place to prevent these issues from occurring – or at the very least to minimise the problems that they will cause.

Running a successful audit

Due diligence takes time and effort from both sides of the process. It will involve a number of auditors poking into dark corners of your data and many people from your company running around trying to find reasonable answers to their questions. To avoid a complete descent into chaos it is important to plan as much as possible beforehand.

A due diligence investigation is just like any other project your company will perform in that you need to have project management in place. Block out the time required for the audit, being sure to include space for coffee breaks and lunch. Hold a kick-off meeting with the investigators before everything starts so that everyone can see each other. In general, aim to hold in-person meetings wherever possible – although email and teleconferences are useful, nothing solves problems or issues quite as well as face-to-face meetings.

Set aside a large conference room or office to act as a 'home base' for the due diligence process. This is usually known as the data room. You can site the auditors here and provide files or data for them to check as needed. As the investigation will involve confidential information, the room should be enclosed to allow discussion of results without the threat of others overhearing.

The audit process itself usually runs most smoothly when a single person is designated the 'contact point' for due diligence questions. They should take the question or request from the auditors and then take it to a separate office (often called the 'back office'). Here it will be passed on to other employees and experts who will need to find the requested information and put together the necessary explanations. This simplifies the communication process, allows you to check that the response answers the question, and (perhaps most importantly) keeps all of the chaos involved in preparing responses out of sight of the auditors.

You'll need to answer auditor questions quickly, so make sure the various experts involved have the free time to do so. This may mean freeing them from their usual tasks to obtain the necessary time – be sure to find support or extra workers so that the daily work of the company does not come to a halt.

One thing you should not forget is that the due diligence involves both sides *working together*. It is not a competition, nor are you trying to sneak terrible results past the auditors. Although it may seem like a good idea (every program has problems, after all), these will inevitably be discovered and will poison the rest of the negotiation process. Be open about issues, discuss them and your planned responses.

Typical mistakes

There are a number of mistakes that you will see during a scientific due diligence investigation. Here are a few of the most common ones and how to avoid them.

Hiding information

Due diligence relies on openness and transparency between the two parties. In particular, the investigating company will expect that they will have access to all data and results – *without* gaps or missing information. It is often very tempting to 'forget' the outcome of a study, or perhaps to fail to mention a few key but unflattering results. This kind of forgetfulness is amazingly common amongst companies with less-than-ideal results or development programs.

Resist the temptation to leave information out of the audit, and never, ever try to hide data. You may get away with it (sometimes several times), but inevitably someone, somewhere, will figure out that you have been sneaky. When they realise this, you will (a) kill the hopes for licensing or acquisition and (b) be chased by well-paid and angry lawyers. It's not worth it. Be transparent.

Not planning

Just like any audit, due diligence inspections are a disruption to your normal activities. People will be running back and forth, experts will be stressing over presentations, you will need to send litres and litres of coffee into the audit room. This is natural. But you can minimise the disruption involved by planning ahead – plan the location where it will occur, plan the timing of the audit, plan the people required and plan their schedules to provide space. This is particularly important for small teams, where the people will need to split their time between the due diligence process and actually running their business. Make your life easier by focusing on planning and time management *well before* the audit begins.

Not being organised

Being organised is, oddly enough, an important attribute for a biotech company. Over the course of development you will produce reams of data, hundreds of reports, and a simply ridiculous amount of clinical study information. It is vital that you be able to keep all of these documents organised so that the most recent version of any information can be found quickly and easily.

This is mostly important for you – organisation keeps your company running smoothly and helps answer questions with ease. But it is also vital for the due diligence process. You will receive a number of requests for information from the auditing company, these will need to be answered as quickly as possible. Slow responses look very unprofessional – not being able to find the requested data looks even worse. Do yourself a favour and keep your information as organised as possible.

Not explaining

You get a request for a report from the auditors. It is a complicated document, with some slightly uncommon data analyses due to various confounding factors. You find it quickly (because you are organised) and bring it into the office. You hand it over, and walk out. The auditors go over it and are horrified at the non-standard statistical approach, they demand more information.

What did you do wrong? You handed over information without having someone there to *explain* the information.

Always have an expert available to provide an overview of the information being provided, including any unique areas which may need better explanation. This may be a slideshow, a quick chat, a written memo – the important thing is that some sort of context is provided. This allows you to avoid the kind of misunderstanding that would otherwise take up hours of pointless discussion.

Not identifying a lead candidate

Many start-up companies in early development will produce a list of molecules with an effect on their system of interest. This is not a lead candidate molecule! A true lead will be a molecule with the characteristics of a potential drug, it will have been evaluated within the company and a decision made to progress it through the development process – a decision made on promising early results. Far too many people get excited about the effects they see in screening or in vitro tests, they fail to ask themselves 'will this make a good drug?'

Don't forget about CMC

Clinical trials tend to hold the major share of everyone's attention – they are big, flashy and expensive. Yet you cannot hold a clinical trial if you can't make the drug. One factor which separates big pharma from small biotech firms is the knowledge of manufacturing and quality control – both of which are vital for the final product (particularly when developing new biological therapeutics). You should always keep the final need to manufacture your drug in mind, even during the initial development stages. This means that there should be a proper plan for determining the final formulation in place- and that this plan should be followed closely. Mistakes or suboptimal decisions in the formulation development stage can have highly expensive consequences at a later date.

Not finding biomarkers

Biomarkers are biological indicators of a disease state or the action of your drug. They are extremely important for your development process as they allow you to identify whether the drug is having an effect *in vivo*. Although they may only be tangentially related to the final goal (curing disease), a surrogate biomarker allows you to estimate efficacy *prior* to running large, expensive clinical trials. Not having a biomarker is often considered a deal-killer by many investment firms – the inability to assess efficacy at an early stage simply creates too much risk.

Failing to assess the competition

You have a new wonder drug, one which will change the face of medicine forever. That's great. But what are your competitors doing? No medicine is developed in isolation, there are always other companies in the space or other drugs with overlapping patient populations. You need to be able to clearly describe how your drug is different to those of your competitors, both positives and negatives, and how you intend to address or exploit these differences.

Not having correct IP protection in place

Intellectual property is important, it underlies the high-tech economy of biotech and pharmaceuticals. *Protecting* that IP is just as important – no-one wants to spend years developing a new miracle drug only to have someone copy it and steal their profits. Because of this, it is essential that companies have patents on their key technology before looking for licensing opportunities. Even this is quite late, most start-ups will have patent protection in place before even beginning commercialisation activities.

This means that your company should *absolutely* have IP protection in place prior to due diligence. You should have patents for your technology or licensing agreements for the technology of others, these should be air-tight and should cover all of your key process steps. You should also ensure that a patent owned by the company founder has been licensed *to the company itself* – this is important for further licensing but tends to be forgotten in the excitement of founding.

Lack of communication and documentation

Audits are a confusing, stressful event in which many different actions are happening simultaneously. This often leads to misunderstanding, be it at the time or several months down the track. When hosting an audit, you should be sure that everyone knows how the information flow should occur – who is the main contact, who contacts the experts, who ensures the requested data is provided, etc. You should also ensure that everything is documented – this includes requests, information provided, or discussions between the parties.

This may seem like overkill, but keep in mind that the people involved will change over time. Arguments over Phase III trials may hinge on an agreement made in discussions three years earlier, at which point you'll be very thankful that those meetings were properly documented.

Chapter 13: Appendix II - An example checklist of questions

It helps to come prepared to a due diligence investigation with a list of questions to ask and follow-up on. The following chapter provides a basic list of questions which will be relevant when performing scientific due diligence. Be aware that every investigation is different and thus it will undoubtedly be necessary to customise this list for your specific situation.

Regulatory questions

- What exactly is the drug being examined? Is it a new chemical/biological entity, a generic, a device, etc.?
- Do you have a listing of the current regulatory approval status and planned status?
- Have submissions for clinical trial applications been prepared and submitted?
- Who is the sponsor of each application?
- Has institutional review board approval been provided?
- Have all investigators signed the appropriate forms?
- Has informed consent been obtained?
- Were any deficiency letters received? If so, what was the response?
- Does the latest version of the investigators brochure contain recent, non-obsolete information? (i.e. is the data given to the authorities up to date?)
- Is the drug likely to be approved for the desired indication?
- Does the development plan appear reasonable?
- What other competing products are in development or on the market?
- Does the submission strategy make sense?
- How does the submission strategy match up with comparable products?
- Do you have access to all minutes/correspondence from scientific advice meetings? Have recommendations been made? Have they been followed?
- Does the development and regulatory plan match up with appropriate guidance documents?
- If not, is there a reasonable justification for ignoring the guidance?
- Does the drug qualify for a special category such as an orphan drug or priority review?
- Will the drug be approved via the mutual recognition or the centralised procedure?
- Has the company paid all of the required user fee charges?

Quality

- Is there an SOP for writing, handling, and updating SOPs?
- Are all documents passing through the appropriate review and approval procedure?
- Are distribution records maintained for all GMP-relevant documents?

- Is there a procedure in place to ensure that the most recent version of a document is being used?
- Do GMP-relevant documents include a history of changes for traceability?
- Are GMP-relevant documents being archived for later retrieval?
- Including those ones which are now obsolete?
- Are documents being filled in correctly, including dates and the name of the person performing the entry?
- Does a master batch record (MBR) exist?
- Does the MBR describe the equipment to be used, the process steps, the process parameters and in-process controls?
- Does the MBR have space to record deviations and results?
- Is there a change control system in place? If it is a contract manufacturer, is there a system to ensure that the changes will be reported to the customer?
- Are analytical processes in place to ensure the quality of the product?
- Are these checked by QA prior to release of the product?
- Is there a system in place for handling deviations and OOS events, including an approach to issue corrective and preventative actions afterwards?
- Have you obtained an assurance that no person involved in the project has been debarred by the FDA or convicted of a felony for a crime relating to drug development or approval?

Chemistry, manufacturing and controls

- Is the current manufacturing process suitable for your company?
- Will your company need to manufacture it in their own facilities, via a contract manufacturer, through the original licensors' facilities?
- Do the necessary contracts already exist or will you need to approach other companies to determine costs and availability?
- Will technology transfers between sites be involved, with their extra associated costs and validation requirements?
- Is the active substance already being produced by a contract manufacturer?
- If so, do you have access to the DMF or ASMF, or extracts thereof?
- Do you have a copy of the quality agreement?
- Do you have access to the site master file?
- Does it provide a reasonable overview of the manufacturing site?
- How reliable is the manufacturer?
- Are they used by other pharmaceutical companies?
- What is their general reputation?

- Are the manufacturing facilities in compliance with GMP?
- Do they have a GMP-certificate granted by a reliable health authority?
- When was the last health authority audit performed?
- What was the result?
- Were any observations made, and if so – what was the response?
- Are the analytical methods in place the correct ones?
- Have they all been validated?
- Do they match pharmacopeia requirements?
- Are the correct reference samples in place?
- Do you know what impurities are present in the active substance and final drug product?
- Have they been identified and quantified?
- Have toxicology assessments been performed?
- Is the active pharmaceutical ingredient one which has 'problematic' properties which require extra testing to be performed? Examples here include chirality, hygroscopy (water-absorbing properties), low solubility in water, mediocre stability, or light/temperature sensitivity.
- Are the excipients produced according to pharmacopeia requirements?
- Have the excipients been previously used in medicines with the same route of administration?
- If not, will they need to be filed as a novel excipient?
- Has the data been developed which would support this filing?

Preclinical

General

- Were preclinical studies performed in-house or at a contract research organisation?
- Was the material used for preclinical testing the same (or at least highly similar) as that planned for the clinical trials?
- Do the route of administration and dosing frequency match with the eventual clinical treatment?
- Were the studies performed according to Good Laboratory Practice requirements?
- Has the site at which studies were performed ever had audit observations or compliance failures?

Toxicology

- Was the toxicology study relevant to the planned clinical trials?
- Which dosage or exposure level led to toxic effects in the animals treated? Which doses had no effect?
- What were the toxic effects? Are they different between the single-dose and repeat-dose studies? Were they reversible or permanent following treatment cessation?

- Which organs were most affected by toxic effects?
- Can these toxic effects be linked to the drug itself or downstream metabolites?
- Are the toxic effects typical for the class of drug which is being developed?
- Is there a linear relationship between the dosing concentration and the toxic effects observed?
- What would be a likely safe dosing level in humans?
- Does the data available support the planned clinical dosage, route of administration, and treatment regimen?

Pharmacology

- What routes of administration have been tested in preclinical trials?
- Do they make sense given the drug?
- Do they match the requirements of the patient population and disease?
- Were the animal models chosen suitable for the disease being investigated?
- Could the study guarantee that the correct/representative amount of drug was provided?
- Do the metabolic pathways involved in the animal model match to the pathways occurring in humans?
- Have the studies shown the bio-distribution of the drug throughout the body, both in a qualitative fashion ('the drug is there') and quantitative ('X mg of drug is there')?
- Is the drug even reaching the right place?
- Is it occurring in amounts sufficient to cause a pharmacological effect?
- Which enzymes are involved in drug metabolism and clearance?
- Does this match the expectation?
- What are the ADME kinetics, and do they support the proposed use of the drug?
- How well is the drug cleared from the body?
- Is the drug intended to be used in patients with impaired drug clearance?
- Has a safety factor been built into the required calculations?

Clinical trials

General

- Do you have access to all trial protocols, case report forms, and results? From both completed and ongoing studies?
- Were the trials designed in such a way that they can provide a statistically relevant answer to the question you are asking?
- Was approval from the Institutional Review Board and other bodies obtained?
- Can you ensure that informed consent was obtained?
- Were the trials performed according to Good Clinical Practice?

- Was an audit of the data performed to ensure accuracy and consistency?
- If meetings with health authorities were held, were the issues and suggestions discussed in the meeting addressed or implemented?
- Were any studies terminated, put on hold or withdrawn? And if so, why?
- Are any clinical trials being conducted in foreign countries?
- Has the required information been uploaded to ClinicalTrials.gov?
- Is the indication being sought one which will provide a quick route to marketing approval?
- Would other indications be faster?
- What is the patient population for the currently targeted indication?
- Is this a large population or a niche, orphan-drug-level population?
- What is the indication with the largest patient population that could be targeted by this drug?
- What are the plans to reach this indication?

Phase I

- Are the appropriate assays being used?
- How homogenous or heterogeneous was the participant population?
- Were the initial trial participants part of the eventual target population?
- Were any studies performed in patients with a potentially abnormal response to the drug?
- Was a difference observed?
- How much variability was observed in the measured parameters?
- Were the preclinical studies able to predict the ADME parameters observed in the trial?
- Were any potential drug-drug interactions observed?
- Are any further questions regarding safety open which need to be answered?

Phase II

- Has a reasonable definition of clinical efficacy been used for the trial?
- Was clinical efficacy shown?
- Based on the Phase II results, is there any indication that the new compound is an improvement over the currently available options?
- How many patients will be needed to achieve statistical significance in Phase III?
- What major risks exist when moving to the next phase of clinical trials?

Phase III

- Were the endpoints tested appropriate for the disease in question?
- Did the clinical trial reach the stated endpoints?
- What was the study set-up and what was used as the comparator?

- Placebo or current treatment?
- If a typical treatment was used as a comparator, was the concentration equivalent to normal treatment dosage?
- Have regulatory requirements for the clinical trial been met?
- Do the results support the use of this drug for this disease?
- By how much?
- How convincing is this?
- Does the drug show a significant lead over currently available competitors?

Marketing

- Have you obtained copies of all marketing materials?
- Has the company ever promoted their product for unapproved or off-label use?
- Has the INN been assigned for the active pharmaceutical ingredient (assuming that it is a new chemical entity)?
- Has the proposed trademark / tradename been approved by the relevant health authorities?
- Is there a plan in place to obtain reimbursement from the payers involved, be it the national health authority or private insurance companies?
- Has a cost-benefit/pharmaco-economic study been performed for the drug? Are the results in the drug's favour?
- Does the company perform or plan to perform direct-to-consumer advertising?
- If yes, is this advertising in accordance with health authority requirements?
- Do you have a listing of the current and foreseen competition?
- What are the distinguishing factors between this drug and the current or foreseen competition?
- Are any generic or biosimilar products currently in development or filing which may affect the product?
- Do you know the revenue potential of the new technology?
- What is the size of the total addressable market?
- What is the possibility of penetrating that market?
- Can you estimate the products' gross margin and operating margins?
- Does the drug fit what you are currently doing?
- In other words, will it help improve sales or distribution of your other products, or will you somehow cannibalise your own profits?
- Is the *size* of the deal correct?

- Will it be providing a revenue stream that is close to your current revenue, or is it far larger or smaller?
- If the license is specific to a certain geographical area, does that work with your company's current location or will you need to build up a new marketing and sales division?
- Do you have a sales group with sufficient reach and motivation to market this drug in the defined area?
- Are the expected revenues consistent with our current company size?

Intellectual property

- Has the company provided you with a listing of the patents which have been issued or which are pending approval?
- Which of these are the key patents with respect to the technology?
- Have the required yearly fees been paid for those patents?
- Have you confirmed that these patents have been assigned to the company?
- What opposition to these patents is currently in existence? i.e. legal challenges, patent infringements, etc.
- Have you a list of all the agreements which have been made for these patents – licensing, settlements, etc?
- Does this impact on the proposed licensing approach?
- Has a conclusive prior art search been performed, to ensure that the patents will not be invalidated by previous work?

The 'big' questions

- Is the planned development process scientifically sound? Is it practical?
- Does the development process comply with the required regulations?
- Has a proof of concept been achieved?
- What are the strengths and weaknesses of the compound?
- Does it represent an improvement over the currently available drugs?
- Is the new drug an innovative step forwards, an incremental development, or a 'me-too' drug?
- What are the major negatives or risks of the drug?
- What is the market potential of the drug?
- What is the plan for being paid for the drug?
- How strong is the patent protection?

Chapter 14: Appendix III - An example list of documents

Every investigation is different and thus every due diligence will examine a separate series of documents. However a few of the most typical requests are listed here to help start your check-list.

Regulatory

- Copies of the current dossier
- A listing of upcoming process variations or regulatory commitments which will need to be fulfilled
- A list of products under development and their regulatory status
- A list of filed/approved marketing applications
- Correspondence with health authorities related to marketing applications
- Records showing compliance to post-marketing reporting or study requirements
- A list of drug master files (DMFs) filed by the company.
- Copies of any DMF-related deficiency letters or correspondence
- The most recent DMF annual update reports
- A list of companies authorized to reference those DMFs

Quality

- A copy of the valid GMP Certificate and Manufacturing License
- Contractor quality agreements regarding GMP
- Records of health authority inspections, discussion topics, outcomes, and copies of observations
- GMP manuals
- Standard Operating Procedures
- Listing of other drugs or types of drugs produced on the same manufacturing line as the drug of interest

Preclinical testing

- All preclinical study protocols and reports, including the master study plan and summary report
- Documentation and correspondence regarding compliance with Good Laboratory Practice
- Proof of compliance with regulations on care and use of laboratory animals.

Clinical testing

- Clinical study reports for all completed clinical trials
- Copies of adverse event summaries or reports
- Proof of compliance with Good Clinical Practice regulations.
- Assurance that no services have been provided by persons debarred by the FDA

- Records of clinical trial applications (e.g. application numbers, deficiency letters associated with these applications, correspondence regarding acceptance or denial of approval for clinical trial applications.)

Chemistry, Manufacturing and Control

- Currently valid master batch records
- Specification sheets for raw materials, drug substance and drug product
- If in current manufacture, then a copy of the annual product quality review
- Report detailing the Quality Target Product profile
- Process validation protocol, report, and associated executed batch records
- Stability study reports
- Method transfer and validation reports
- A listing of previously implemented changes, in particular those which have occurred after process validation

Marketing

- Marketing materials from the company
- Recent press releases
- Brochures
- Abstracts or full scientific publications

Intellectual Property.

- All intellectual property which is within scope of the investigation, including products currently being marketed and under development
- A list of patents and patent applications.
- A list of owned trademark and trade names.
- A description of methods used to protect trade secrets and know-how.
- A schedule and copies of all consulting agreements, agreements regarding inventions, and licenses or assignments of intellectual property to or from the Company.
- Any patent clearance documents.
- A schedule and summary of any claims against the Company regarding intellectual property

Chapter 15: Appendix IV - ICH Guidelines

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) published a number of 'harmonised' guidelines. These guidelines are considered to provide a single best-practice approach for quality, safety, and efficacy testing – they are then taken as the basis for regulatory requirements in many different countries. This section lists the current ICH Guidelines, these should be used as a basis for your assessment of potential technology. Essentially, if ICH guidelines have been followed during development, then there is a good chance that the product will get through the regulatory approval process.

ICH Quality Guidelines

Q1A (R2) Stability Testing of New Drug Substances and Products

Q1B Stability Testing: Photostability Testing of New Drug Substances and Products

Q1C Stability Testing for New Dosage Forms

Q1D Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products

Q1E Evaluation of Stability Data

Q1F Stability Data Package for Registration Applications in Climatic Zones III and IV

Q2 (R1) Validation of Analytical Procedures

Q3A (R2) Impurities in New Drug Substances

Q3B (R2) Impurities in New Drug Products

Q3C (R7) Impurities: Guideline for Residual Solvents

Q3D Guideline for Elemental Impurities

Q4 Pharmacopeias

Q4A Pharmacopeial Harmonisation

Q4B Evaluation and Recommendation of Pharmacopeial Texts for Use in the ICH Regions

Q5A (R1) Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin Q5A

Q5B Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products

Q5C Stability Testing of Biotechnological/Biological Products

Q5D Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products

Q5E Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process

Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances

Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products

Q7 Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients

Q8 (R2) Pharmaceutical Development

Q9 Quality Risk Management

Q10 Pharmaceutical Quality Systems

Q11 Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)

Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

ICH Safety Guidelines

S1 Rodent Carcinogenicity Studies for Human Pharmaceuticals

S1A Need for Carcinogenicity Studies of Pharmaceuticals

S1B Testing for Carcinogenicity of Pharmaceuticals

S1C (R2) Dose Selection for Carcinogenicity Studies of Pharmaceuticals

S2 (R1) Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use

S3A Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies

S3B Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies

S4 Duration of Chronic Toxicity Testing in Animals (Rodent and Non-rodent Toxicity Testing)

S5 (R2) Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility

S5 (R3) Revision of S5 Guideline on Detection of Toxicity to Reproduction for Human Pharmaceuticals

S6 (R1) Preclinical Safety Evaluation of Biotechnological-Derived Pharmaceuticals

S7A Safety Pharmacology Studies for Human Pharmaceuticals

S7B The non-clinical Evaluation of the Potential for Delayed Ventricular Repolarisation by Human Pharmaceuticals

S8 Immunotoxicity Studies for Human Pharmaceuticals

S9 Non-clinical Evaluation for Anticancer Pharmaceuticals

S10 Photosafety Evaluation of Pharmaceuticals

S11 Non-clinical Safety Testing in Support of Paediatric Medicines

ICH Efficacy Guidelines

E1 The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life Threatening Conditions

E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting

E2B (R3) Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports

E2B (R3) Implementation: Electronic Transmission of Individual Case Safety Reports

E2C (R2) Periodic Benefit-Risk Evaluation Report

E2D Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting

E2E Pharmacovigilance Planning

E2F Development Safety Update Report

E3 Structure and Content of Clinical Study Reports

E4 Dose-Response Information to Support Drug Registration

E5 (R1) Ethnic Factors in the Acceptability of Foreign Clinical Data

E6 (R2) Good Clinical Practice (GCP)

E7 Studies in Support of Special Populations: Geriatrics

E8 General Considerations for Clinical Trials

E8 (R1) Revision on General Considerations for Clinical Trials

E9 Statistical Principles for Clinical Trials

E9 (R1) Addendum: Statistical Principles for Clinical Trials

E10 Choice of Control Group and Related Issues in Clinical Trials

E11 Clinical Investigation of Medicinal Products in the Pediatric Population

E11 (R1) Addendum: Clinical Investigation of Medicinal Products in the Pediatric Population

E11A Paediatric Extrapolation

E12 Principles for Clinical Evaluation of New Antihypertensive Drugs

E14 The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs

E14/S7B Discussion Group on Clinical and non-Clinical Evaluation of QT/QTc Interval Prolongation

E15 Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories

E16 Biomarkers Related to Drug or Biotechnology Product Development: Context, Structure and Format of Qualification Submissions

E17 General Principles for Planning and Design of Multi-Regional Clinical Trials

E18 Genomic Sampling and Management of Genomic Data

E19 Optimisation of Safety Data Collection

Chapter 16: Appendix V - Glossary and Useful Sources

ADME

An acronym for Absorption, Distribution, Metabolism, and Excretion, it covers the processes by which a drug is taken up by the body, shuttled around, converted to other forms, and removed.

Adverse Event

The unwanted action of a drug – this can include side effects or cases where the drug simply doesn't work. In clinical reporting it is most often used to refer to unwanted side effects and is classified according to severity.

Active Pharmaceutical Ingredient (API)

The part of your final product which has a pharmaceutical effect, typically either a small molecule drug (the 'traditional' molecular compound) or a biological (a protein or similar, significantly larger than small molecule APIs and significantly harder to produce).

Active substance master file

A document submitted to EMA which provides the regulatory authority with confidential, detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of an active pharmaceutical ingredient.

Audit

The systematic and independent examination of an organisation's documents and records, it may be conducted by health authorities, auditors from other companies, or even the organisation itself (known as a self-audit).

Blinding

The knowledge that you are receiving a treatment can affect your response to the treatment, a phenomenon known as the placebo effect. To prevent this from occurring in clinical trials, patients are *blinded* – they are not aware if they are receiving the trial drug, a placebo, or another compound. Double blinding occurs when neither the patient nor the doctor providing the treatment knows what the patient is receiving.

Briefing book

A document provided to a health authority prior to a scientific advice meeting, it contains an overview of the pharmaceutical, the issues to be discussed, and the questions which the applicant wishes to have answered.

Case Report Form (CRF)

A document used during clinical trials, a CRF contains all data which is generated for a single patient in the trial. This includes physician reports, medical test results, adverse events, and even results from post-study follow-up testing. Depending on the trial in question, a CRF can reach hundreds of pages per patient, making for a vast amount of documentation to look through.

Centralised procedure

A process by which a drug can be approved throughout all EU countries after a single submission.

Change control

A formal process by which changes to a registered or GxP-relevant process, facility, or materials may be assessed and approved. It acts to provide a level of control over the number and scope of changes which occur in every process over time.

Chemistry, Manufacturing and Control (CMC)

CMC is a broad field covering the requirements for characterisation, manufacture and testing of a drug substance or drug product.

ClinicalTrials.gov
A web-based database hosted by the National Institutes of Health (NIH), ClinicalTrials.gov provides a host of information on currently-running or completed clinical trials. This is particularly useful when you are examining potential competition or looking for clinical precedents. Unfortunately, some weaknesses do exist. Although all trials in the US are registered when they begin, the *results* of these trials are rarely uploaded once completed. This severely limits your ability to follow-up on interesting findings.

Clinical research organisation (CRO)
An organisation which is specialised in performing clinical studies, usually used to perform studies on behalf of another company. CROs are very useful for smaller pharmaceutical firms which do not have the resources to set up their own clinical groups.

Contract Manufacturing Organisation (CMO)
An organisation which manufactures a drug substance or drug product on behalf of another company. CMOs are very common in the current pharmaceutical industry.

Corrective and preventative action (CAPA)
The outcome of a deviation investigation should be a set of actions that you will take to solve the problem and then prevent it from reoccurring – these are known as CAPAs.

Clinical endpoint
The clinical endpoint of a trial is the parameter which is being measured as a marker of the therapeutics' success. A trial will normally have several of these, divided into primary endpoints (the main focus of the trial) and secondary endpoints (which provide additional information).

Clinical Trial Application (CTA)
The formal request to begin human studies with a new drug.

Clinical Trial Authorisation
Authorisation from regulatory health authorities to take the new medicine into clinical trials. Typical documentation which is submitted would be the Investigational New Drug (IND) dossier in the US, an Investigational Medicinal Product Documentation (IMPD) in the EU and a Clinical Trial Exemption (CTX) in the UK.

Common Technical Document (CTD)
The standard format for the regulatory dossier, it divides the typically required information into a number of standardised modules.

Data protection
The period of time during which generic manufacturers cannot use data generated by the originator to support the safety of their copy of the drug. This does not prevent the generic manufacturer from performing their own clinical trials to generate their own data.

Deviation
When something goes wrong, usually with an impact on GxP. This is known as a deviation, it will then be the focus of an investigation, root cause analysis, and usually results in a number of Corrective and Preventative Actions.

Dosage
The amount of a drug which is provided to a patient, as well as the frequency at which it is provided.

Dose-limiting toxicity
The point at which the side effects of a drug or other treatment become serious enough to prevent an increase in the treatment dosage.

Dossier
The regulatory dossier is a summary of all the information gathered on a drug, the manufacturing process, the control strategy, and various other pieces of information. Often thousands of pages in length, it is submitted to the healthcare authority to obtain permission to market a drug in a particular country. Once approved, it forms a binding contract with the country and thus any changes to the process must be reported.

Drug master file
A document submitted to the FDA which provides the regulatory authority with confidential, detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of an active pharmaceutical ingredient, a drug product, raw materials, or primary packaging.

Drug product (DP)
The final drug which will be provided to patients.

Drug substance (DS)
The active pharmaceutical ingredient plus any other supporting chemicals, this will then be compounded with the excipients to form the drug product.

Drugs@FDA
https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm

The Drugs@FDA database provides information on therapeutic products which have been approved by the FDA, with records dating back to 1939. This includes usage and approval registrations, as well as copies of FDA correspondence with the marketing authorisation holder which can help identify FDA thinking on specific topics. Useful for getting an overview of US-registered products.

Due diligence
The investigation of a business or technology prior to signing a contract, used in this book to refer to the investigation prior to licensing or purchasing pharmaceutical/biotech intellectual property.

Enabling technology
A technology which allows other inventions or discoveries to be built upon it. A typical example from recent years would be the CRISPR/Cas DNA-editing technology.

European Medicines Agency (EMA)
The central health authority of the European Union.

European Public Assessment Report (EPAR)
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp

A full scientific assessment report of a medicine authorised at a European Union level, albeit one which has been heavily simplified and censored to match the public nature. An EPAR document is published by the European Medicines Agency for every drug which is authorised in the European Union. The EPAR contains information on the drug, its approval conditions and other scientific information. The database also provides selected clinical trial data for drugs approved after 2016, which can be extremely helpful for comparison purposes.

Excipient
Compounds present in the final drug product which are not the active pharmaceutical ingredient. They may be inert or have an effect on the pharmacodynamics of the drug.

Exclusive Licence
The sole right to use a piece of technology, to the exclusion of all others.

Exclusivity
The time period in which other companies are prevented from competing with a drug already on the market. This protected time is separate to that granted by a valid patent, instead being related to the drug approval process.

Executed Batch Record
The 'filled in' batch record, with all of the times, measurements, observations, etc. clearly recorded and signed off. This is the official record of the production process and thus should be archived correctly – particularly when related to process validation runs or other regulatory-relevant manufacturing campaigns.

U.S. Food and Drug Administration (FDA)
The health authority of the United States of America.

Formulation
The nature of the drug product, including the ingredients, amounts thereof, and overall presentation.

Freedom to operate
A legal opinion as to whether a product, process or service may be considered to exist without infringing on any patent or patents owned by others.

Good Clinical Practice (GCP)
A set of guidelines covering the best-practice methods for performing clinical trials, with requirements for documentation, informed consent, and scientific rigorousness.

Good Laboratory Practice (GLP)
A set of guidelines covering the best-practice methods for scientific studies. Many of these overlap with GMP requirements, the main difference being the degree of oversight from quality assurance.

Good Manufacturing Practice (GMP)
A set of guidelines covering the best-practice methods for manufacturing of pharmaceuticals and related materials.

Guidance document
A document published by a health authority which describes their current thinking on a topic. In general, pharmaceutical companies should attempt to follow the guidance laid down in these.

Hits
Compounds identified during drug screening which appear to have an effect on the chosen target.

In-process Control (IPC)
Measurements of variables during production which are used to monitor and control the overall process.

Institutional review board (IRB)
An institutional review board (IRB) is a type of committee that reviews the methods proposed for a research program (most importantly a clinical study) to ensure that they are ethical. IRB approval is a must prior to beginning a clinical trial.

Investigators' Brochure
A comprehensive document summarizing the body of information about an investigational drug, it is extremely important throughout the drug development process and is updated with new information as it becomes available. The brochure compiles data from preclinical or clinical trials which may be relevant to studies of the investigational drug in human subjects – it is designed to provide the 'investigator' in a clinical trial with the information they need.

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)
A group which comprises representatives from the European, Japanese and United States health authorities as well as experts from the pharmaceutical industry. The group discuss scientific and technical aspects of pharmaceutical product registration and create harmonised guidance documents which can be used in any of the partaking countries.

International non-proprietary name (INN)
The official generic name given to a pharmaceutical using a standardised naming system. It is in contrast to a trade name or brand name in that the INN is used by both originator and generic manufacturers.

Investigational Medicinal Product (IMP)
A drug being used within a clinical trial, as defined by EMA

Investigational Medicinal Product Dossier (IMPD)
A dossier required prior to receiving approval to perform clinical trials in the European Union.

Investigational New Drug (IND)
The program overseen by the FDA by which a drug gains approval to be used for clinical trials.

Joint venture
A business entity created by two or more parties for a defined purpose. It usually consists of shared ownership, shared returns and risks, and shared governance.

Key opinion leader (KOL)
A leading figure within the healthcare industry, whose opinions (including those on pharmaceutical products) are able to influence their peers.

Lead compound
A compound which has shown promise in early drug development studies, and is now ready for more strenuous testing.

Letter of authorisation
Permission from a DMF holder for a pharmaceutical company to refer to the information provided in the DMF rather than including it in their dossier.

Licensee
The party who is intending to obtain a license to use intellectual property from the licensor.

Licensor
The licensor is the holder of rights to the technology, and is intending to license it out to other firms.

Marketing Authorisation
The official confirmation from a health authority that you can sell your pharmaceutical.

Marketing Authorisation Application
The application required to obtain marketing authorisation. This is a long and drawn out process.

Marketing authorisation holder
The official holder of the marketing authorisation. Note that this is often different to the parent company, particularly in cases where an international firm has multiple country-specific organisations.

Master Batch Record (MBR)
The not-yet-filled-out record containing instructions for all steps in the production process. A copy of this will be filled in with measurements and check-lists during manufacture, this will then be known as an executed batch record.

Milestone Payment
Payment received once a particular point in the development process has been reached, such as a successful Phase II trial.

Mode of Action
The manner in which a drug exerts its effects.

Mutual recognition procedure
A drug approval route in the European Union by which one member state will assess the marketing authorisation application, after which other states will accept this finding for their own region.

New Chemical Entity (NCE)
A compound in which no active moiety (active part of the compound) has been previously approved by the FDA.

New Drug Application (NDA)
The application to the FDA to receive marketing authorisation for a new drug.

Non-inferiority
The drug being compared is not worse than the other drug.

The Orange Book
https://www.accessdata.fda.gov/scripts/cder/ob/

The Orange Book (properly known as the *Approved Drug Products with Therapeutic Equivalence Evaluations*) provides information on drugs which have been approved by the FDA. This includes patent and exclusivity information, which allows you to identify timelines for generic competition.

Orphan drug
A specialised designation for drugs which treat rare diseases, those which only affect a small portion of the population. Orphan drugs receive various bonuses and advantages to offset the reduced revenue available from the small patient population.

Package insert
The leaflet which comes inside the box that the drug is delivered in. The contents of the package insert are often a matter of significant argument between the pharmaceutical company and the health authority.

Paediatric Investigation Plan (PIP)
A development plan which is intended to ensure that enough studies are done to allow approval of a drug for children. The contents of the PIP are a matter for discussion and eventual agreement between the pharmaceutical company and the EMA. In the EU, all marketing authorisation applications need to have results from the studies which were laid out in the PIP. Exceptions occur, the medicine may be exempt (when it is not safe for children) or given a deferral (when data from adults needs to be gathered first). The PIP requirement also applies when adding new indications or routes of administration to a currently-approved drug.

Patent
The legal right to exclusive commercial use of an invention. This is provided in exchange for providing a detailed description of the invention, which reverts to the public after the patent expires.

Patent thicket
A large number of patents with slightly different claims which serves to block generic competition to a pharmaceutical even after the original patent has expired.

Payer
The organisation that actually pays for the drug, normally a government health department or a health insurance company.

Pharmacopeia
A comprehensive listing of testing methods and required specifications which should be used to ensure the quality of pharmaceuticals and raw materials.

Phase I-IV clinical trials
The different stages of clinical trials, where the number of enrolled patients, importance, and costs increase dramatically with each stage.

Pre-approval inspection
Prior to approving a drug for the market, health authorities such as the FDA or EMA will inspect the manufacturing facility of that drug to ensure that it fulfils GMP requirements.

Pre-clinical studies
Determining safety and efficacy of a candidate drug via animal trials.

Prior art
The information which has been made available to the public prior to the filing of a patent.

Process characterisation
The act of performing numerous tests on your manufacturing process to see what variations lead to which changes in the final product or result.

Process parameter
A measurable variable in the manufacturing process which has an effect on attributes of the final product.

Process step
The individual actions which a manufacturing process can be broken down into.

Process validation
The act of proving (and documenting) that your process is highly reproducible and leads to a high-quality final product. This is normally performed through the manufacture of three commercial-scale batches and is a hard requirement for regulatory approval of a manufacturing process.

Quality adjusted life year (QALY)
A way to compare healthcare interventions – a perfectly healthy year of life is 1 QALY, a year of being dead is 0, and various degrees of illness come somewhere in-between.

Quality agreement
A quality agreement is a comprehensive written agreement between parties involved in the contract manufacturing of drugs that defines and establishes each party's manufacturing activities in terms of how each will comply with Good Manufacturing Practice.

Quality assurance (QA)
The group within a pharmaceutical firm who have final oversight over the quality of all aspects of the drug.

Quality attribute
An attribute of the final product or intermediary which is related to the overall quality of the drug. These are ranked by importance, those with the greatest impact on final drug product quality being known as critical quality attributes.

Qualified Person (QP)
The qualified person is responsible for the final decision to release a batch to the market. Under European Union law, they are personally liable for failures of quality and may even serve jail time as punishment.

Quality Target Product Profile (QTPP)
The desired final product and its desired quality attributes. The QTPP can be thought of as the end goal of a development program.

Randomised clinical trial
A clinical trial in which patients are randomly assigned to a treatment arm. It is considered the gold standard for determining drug efficacy.

Request for Information (RfI)
The response a regulatory health authority sends when they are unhappy with something and would like to get some more information. Also known as a Deficiency Letter, these are common but nonetheless stressful to answer.

Royalty
The process by which a set percentage or amount of each sale is returned to the inventor.

Safety profile
The chemistry, pharmacology, therapeutic effects, and adverse effects of an administered drug or other substance.

Scale-up
The act of moving a manufacturing process from a smaller scale (such as small fermenters in the laboratory) into a larger scale (such as ten-thousand litre commercial manufacturing plants).

Scientific advice meeting
A meeting with the health authority to request guidance on certain decisions or aspects of the development and clinical trial process.

Screening
Examining many thousands of compounds to find those with a potential effect on your chosen target.

Self-audit
An audit performed by a company on itself to ensure that the required standards are being maintained.

Site master file
A document prepared by a pharmaceutical manufacturer containing GMP-relevant information about the production and control of pharmaceutical manufacturing operations carried out at the named site.

Specification
The requirements which a drug, raw material, or packaging material must meet to be considered fit for use.

Spin-off company
A company started by an academic institution or academic researcher with the intention of commercialising a discovery made during basic research.

Stability testing
The process of leaving a number of samples in storage for a long period of time to ensure that the product degrades in the expected manner. This will normally be performed at the intended storage conditions as well as at a higher temperature to increase degradation rates.

Standard operating procedure (SOP)
A set of rules to ensure that processes are performed the same way every time.

Summary of product characteristics (SmPC)
A document which is provided alongside the drug in the EU, the SmPC contains more information than the standard package insert and is intended to help physicians with their prescribing decisions.

Summary review/summary basis of approval
A document which contains a summary of the safety and effectiveness data and information evaluated by the FDA during the drug approval process.

Surrogate endpoint
A parameter which allows you to measure the effect of a specific treatment, one which is believed to correlate with a real clinical endpoint.

Technology transfer
The formal process of taking a manufacturing process at one location (or on one line) and implementing it at another.

Term sheet
A non-binding agreement setting forth the basic terms and conditions under which an investment will be made, and which then serves as a template to develop more detailed legal documents

ToxNet
https://toxnet.nlm.nih.gov/

ToxNet provides a wide range of information on the toxicological effects of many chemicals and drugs, thus making it essential for checking potential toxicity effects for drug classes under investigation.

Trademark
A recognizable sign, design, or expression which identifies products or services of a particular source from those of others.

Trade name
The 'brand name' of a drug, which is specific to one manufacturer. This is distinct to the INN, which is shared by all manufacturers of the same drug.

Treatment arm
A group of clinical patients who are receiving a specific treatment, different arms normally receive different drugs or dosages.

Upfront payment
A chunk of cash paid prior to commencing a project, as a way to defray expenses or to show the seriousness of the deal.

US Code of Federal Regulation (CFR)
The legal regulations of the US federal government. Laws relating to the FDA fall under CFR Title 21, requirements listed here are considered to be absolute requirements for pharmaceutical companies.

Validation
The act of checking your processes to see if they consistently work as they should.

Chapter 17: About the author

Originally from the sunny shores of Australia, Nathan has worked in pharmaceutical companies based in many parts of the world. A varied career has given him a wealth of knowledge regarding the due diligence process and licensing within the biotech field. This handbook represents a compilation of those years of experience, written to help those up-and-coming investigators to get their bearings.