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DRUG DEVELOPMENT FOR START-UPS

While developing a new pharmaceutical product is one of the most interesting and rewarding activities to partake in, it is also extremely challenging. It is a given that drug development projects will not always succeed and the more innovative they are, the higher the likelihood of failure. There is no way to eliminate the risk of failure. However, there are ways to reduce these risks.

Traditionally, large companies have dominated the drug discovery and development space, however there are now many smaller pharma and biotech companies experiencing huge success in early discovery. Quite a substantial number of these progress their projects to at least clinical proof of concept prior to out-licensing the product to big pharma. In many cases, when the product is for orphan treatment or niche products, small companies have successfully developed their products all the way to the market. As smaller start-ups and biotech companies enter the development space, creativity and innovation are subsequently increasing. It has also meant that a lot of organisations are entering drug development with limited experience in the area, despite being experts in drug discovery.

Often, drug development and drug discovery are coupled together and viewed as the same, when in fact, they are completely different. For this reason, many start-up companies need to understand more about the basics of drug development. In this paper, we explore the drug development process and how the risk of substantial delay in the development timeline or failure can be reduced.

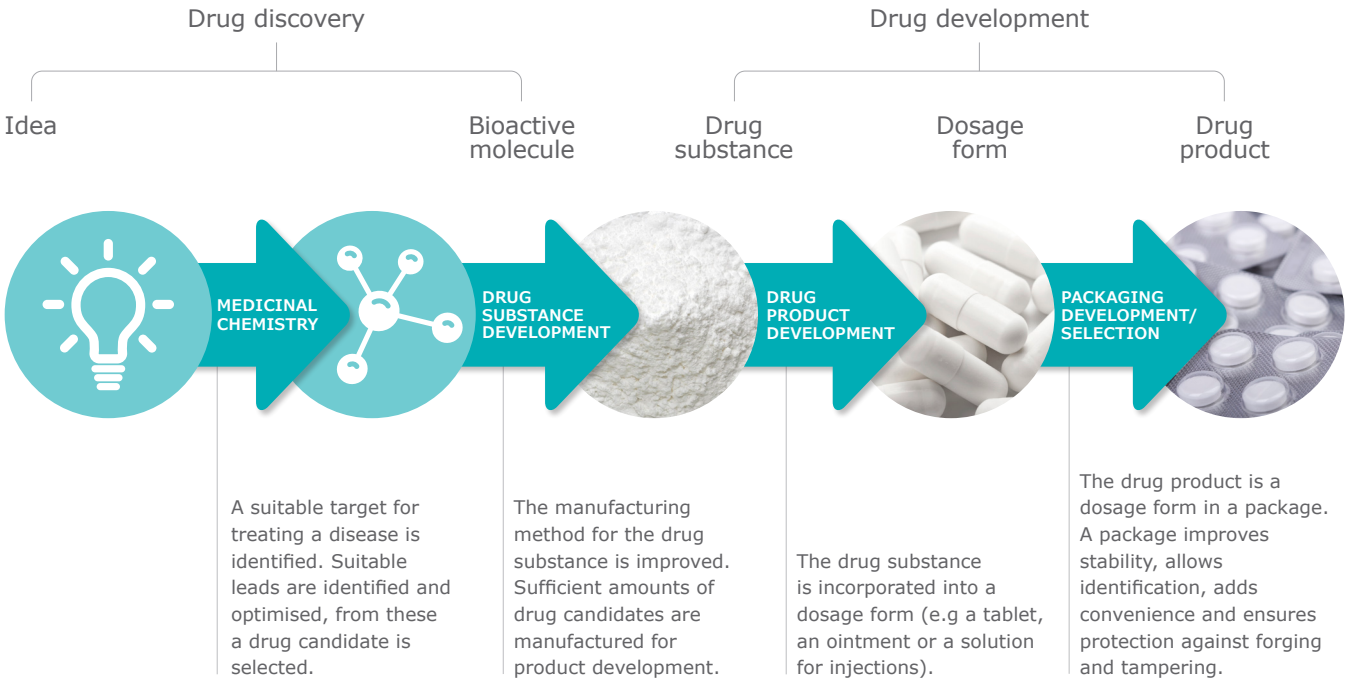

Figure 1: Pharmaceutical development from idea to drug substance to drug product.

WHAT IS A DRUG PRODUCT?

While drug discovery involves progressing an idea to a drug candidate, drug development focuses on progressing the drug candidate to become a new pharmaceutical product on the commercial market (See *figure 1*).

When thinking about a medicine, most people involved in drug discovery focus on the drug substance also known as the active pharmaceutical ingredient/drug substance (API/DS), a small or large molecule that has a certain effect on a biological system. However, a pharmaceutical product is not just an active compound – it comprises of an API/DS that is formulated into a dosage form, which is subsequently contained in a suitable package (See *figure 2*).

Figure 2: A drug product is an API/DS in a dosage form contained within packaging with documented safety and efficacy. Most of the development effort is spent on documenting safety and efficacy in order to attain regulatory approval. The dosage form is still extremely important for therapeutic effect and convenience.

The dosage form and package should not be considered as less important. They typically affect pharmacokinetics, variability, side effects, stability, convenience and cost, meaning they will have a profound impact on therapeutic effect, safety and the profitability of a drug product.

It's essential that a product and its API/DS can be manufactured at commercial scale. When manufacturing in large quantities, the development process needs to have manufacturing and control methods that are suitable for large-scale equipment, are reproducible and give an acceptable cost of goods.

Moreover, safety, efficacy and quality must be carefully documented so that the relevant information can be approved by authorities in different countries. In fact, most of the development work is performed in order to produce the right documentation. As part of the approval process, you must also be able to prove that you have done all the right things. Pharmaceutical development can also be viewed as the process of documenting safety, efficacy and manufacturability in safety studies, clinical studies and tech transfer as described in *Figure 3.*

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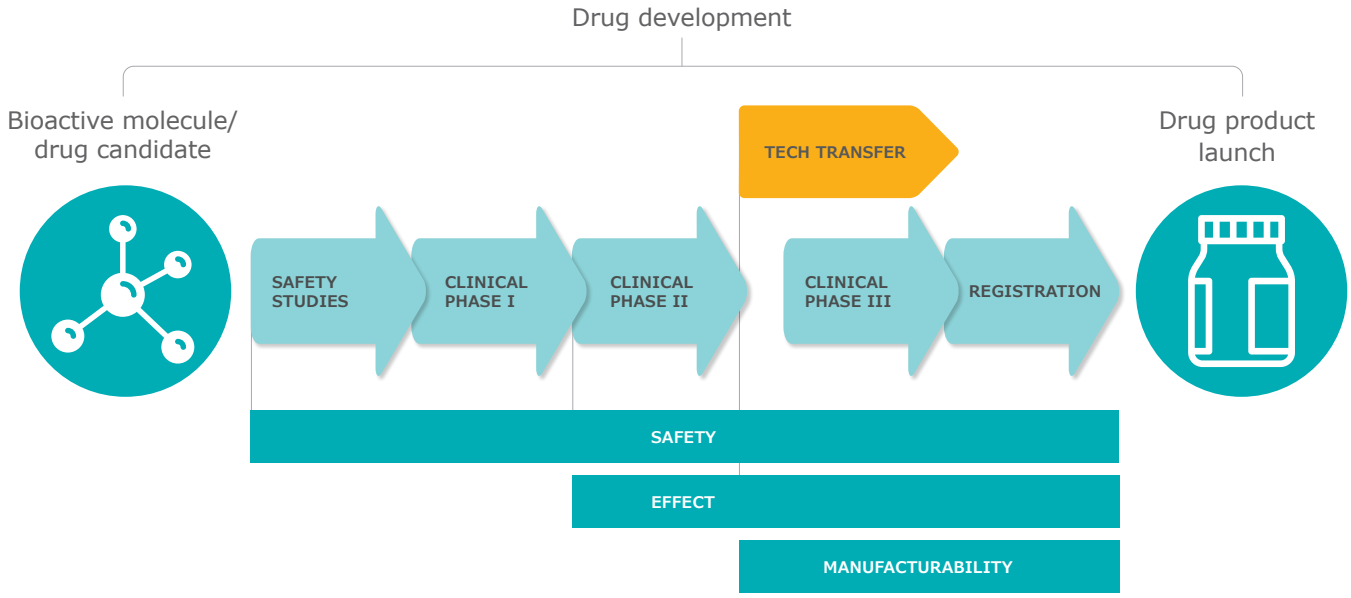

Figure 3: Drug development can be seen as the process of demonstrating safety, efficacy and manufacturability.

As *figure 3* shows, the API/DS was already in focus during drug discovery. However, this does not mean that it can be ignored in the development phase. As part of this process, it is essential that factors such as solid-state characteristics and impurity profiles are defined. Moreover, a manufacturing process that is suitable for large-scale production must be established. It is also extremely important to control the quality of an API/DS as well as drug product, meaning specifications and control methods must be developed.

START WITH THE END PRODUCT IN MIND

Before developing a drug product, it's important to consider what it is you want to achieve and define the required product characteristics. This includes establishing a Target Product Profile (TPP). By identifying where it is you're heading with the project, it can help you overcome two difficult hurdles experienced at the end of development – regulatory approval and market success.

Initially, a business plan should be in place. Questions you may want to answer as part of your plan include:

- How much will we spend on development?
- How big are the future revenues and when will they come?
- What does the market look like?
- Who are the competitors?
- How likely is success?

The business plan equips you with a strategy to guide the process.

All pharmaceutical products require market authorisation in the countries they will be distributed and sold in. In order to increase the likelihood of regulatory approval, comprehensive documentation of the product and its development is required by the regulatory authorities.

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As any mistake may result in a dismissal or a costly delay, a regulatory strategy should be carefully developed along with an expert at the initiation of drug development.

Patent strategy

To recover all development costs, it is vital that the product can be sold with a degree of exclusivity during a certain period. Market authorisation can provide a limited exclusivity but far more effective protection is provided by patents. As patents are based on new inventions, it is difficult to build a detailed patent strategy beforehand. Nevertheless, patent strategy should be considered or revisited at the start of the development phase. At a minimum, the available protections through patents or patent applications for the API/DS need to be thoroughly evaluated.

In general patents on the API/DS offer the strongest protection but patenting the process, salt form, solid-state form, dosage form and similar could provide valuable additional protection and often prolong exclusivity after expiration of the API/DS patent. If there is no or weak protection for the API/DS an additional patent application will be more important. In this case, the development work should be regularly reviewed for possible patentable innovations and they should be evaluated in terms of business value. Usually, numerous problems are solved during development work where patent applications could be filed and granted. Unfortunately, most of these would not be effective at building exclusivity and hence they have little business value. It is also advisable to consider the risk of competitor products blocking your freedom to operate. Patent law can be abstruse, and a patent attorney should be consulted in these matters.

Exit strategy

For most small companies, their business plan will also comprise an exit strategy as developing a drug all the way to launch and marketing it yourself is often an overwhelming task. In many cases it is more attractive to develop the product to a certain point, such as phase IIa. Out-licensing the project at an earlier timepoint will reduce the risk of failure but of course the profit will also be lower. This does not mean that a small company should not consider taking a product through the later development phases to launch. The value of a project at the time of the exit will be based on milestones and the chances of success, which will increase if all development activities are performed with the end result in mind. The TPP will point out the direction during development, and it will also make it possible to estimate a potential market share, target price and ballpark manufacturing and development costs that are needed to prepare a business case.

GETTING INTO HUMANS

In drug discovery, we try to understand safety and efficacy by working with various models. Enzymes, cell models, animals and computer models are all indispensable tools. However, at the end of the day they are just models. Drug development is focused on the actualities: efficacy and safety in humans (unless you are developing veterinary products, of course). We will not know if a product works until it has been tested in humans and regulatory authorities will not approve a product unless there is convincing human data.

Safety studies

Before testing our drug in humans, it is essential to provide evidence that it is safe in two animal species (one rodent and one non-rodent mammal). This evidence is gathered through conducting safety studies that follow Good Laboratory Practice (GLP). Safety studies are costly, take a relatively long time and the results obtained often cause the termination of drug development projects. Hence, it is vital to choose a safety study provider wisely and spend enough time on planning a safety program together with their toxicologists.

Safety studies require API/DS that is manufactured according to defined quality standards and they require quantities that are significantly larger than in the earlier phases. Two things are crucial about the API/DS for safety studies - the quantity and the purity. Prior to ordering API/DS, the study design must be agreed with the toxicology lab. Additionally, API/DS will be required for other tests, so it makes sense to produce quantities for this at the same time. Increasing the batch size a little is significantly less costly

than ordering a second batch at a later time, meaning it is important not to underestimate the need. Usually, a few kgs are manufactured at this stage.

Pharmaceutical scientists are usually interested in high purity but at this stage it is different. The safety studies should be performed with a purity profile that is the same and not more pure than later batches that will be used in humans. This is because new impurities or a higher level of impurities have the potential to cause hazards that would not be identified during safety studies. This also means that it is important at this stage to develop analytical methods that are suitable for assessing purity.

Human studies

Human studies are performed in different phases: Clinical phase I, II and III. In the first phase, a suitable formulation of increasing doses of API/DS are tested in a small number of healthy volunteers. The following step includes testing the effect in a limited number of patients (also referred to as phase II) and eventually in a number of patients that is large enough in order to generate statistical data to allow the drug to be approved by regulatory authorities (phase III). There can also be a phase 0 that is performed on subtherapeutic doses and phase IV that is performed after market authorisation is obtained. Later phases are usually performed as blinded studies where the product is compared either to a placebo (an inert product without effect) or a comparator product. If possible, studies will be performed as double-blind trials meaning that the tested products and comparator/placebo are marked with codes and neither patients nor the physicians know which medicine is which.

The clinical studies are the most time consuming and costly part of a drug development project. It is paramount that the clinical program is carefully planned together with experts in both clinical trials and regulatory affairs. At the same time, it also important to plan for supply of clinical trial material (CTM) as lead times are long and may cause delays. The CTM consists of drug product, that is an API/DS formulated into drug product in a package.

The API/DS has already been manufactured for safety studies and the same or a similar batch size is often suitable for the first clinical studies. However, the API/DS (as well as the drug product) are manufactured with higher quality standards for use in humans so it is usually necessary to manufacture a new batch. It is not possible to make significant changes to the manufacturing method used for safety studies as that could result in other impurities than those present in that stage. It is costly and time consuming to order additional CTM if needed and it is usually better to order a larger quantity from the start.

The dosage form used in clinical studies needs to be decided in collaboration with the clinical trial expert and formulation scientists. In Europe, drug products for all clinical trials must be manufactured according to GMP. The drug product in phase I does not need to be identical to the product to be marketed. Factors such as manufacturing costs and convenience for patients become more important when considering the commercial product. On the other hand, dose flexibility and short development time is more important in phase I. In general, it is also advised to not overdo development in phase I as most drug development projects do not survive early clinical development.

That being said, it is important to have a clear idea of what the intended final product will look like when designing the test product. The development of CTM for phase I is also an opportunity to gather knowledge that will be useful in later stages of development. For example, stability is usually not a problem in phase I as the studies are short and the product can often be stored frozen if needed. However, some stability data is required at this stage and this is a chance to detect potential stability issues at an early stage.

A minimum requirement is that the test product uses the same administration route as the final product. In most cases, the oral route is desired and then simple formulations such as powder in a bottle or powder in capsules can be used. Drug in bottle (DIB) is the simplest, most cost effective and quickest approach. Minimum development and GMP manufacturing are required. This type of formulation is only possible for API/DS with a sufficient aqueous solubility allowing the highest dose to be dissolved in an appropriate amount of water as there is little opportunity for solubility enhancement. In the case of a placebo-controlled study, matching colour and taste is a challenge. Drug in capsule (DIC) requires only limited formulation development. Pure API/DS is filled in capsules manually or using semi-automatic capsule filling. Generally capsule sizes from ‘’00’’ to ‘’4’’are used. Again, the approach is only suitable for highly soluble drug.

In other cases, it may be important to use more elaborate products e.g. to ensure that a poorly soluble drug is absorbed. This approach has the advantage of potentially speeding up development in later stages of clinical testing by reducing or eliminating the need for a bridging bioequivalence study. It also enables speedier delivery of stability, validation and launch batches. Often formulated capsules are chosen but tablets can also be used. The disadvantage of this formulation development approach is that more development work is needed even though it should be emphasised that the formulation development is much less than for a final formulation, i.e. for the commercial product.

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CTM for other administration routes than the oral route are developed when needed. Parenteral solutions are of course used for drugs that are intended for injection. However, intravenous administration is also used in clinical studies for drugs that are intended to be given orally as it is good way of studying the systemic effects. Additionally, the oral bioavailability is determined by comparing plasma profiles after oral and intravenous administration of the drug. Creams, ointments, eye drops or inhalation products will be used when needed. In any case, development and manufacture of CTM is relatively time consuming. Especially, when going into phase I it is common that discussions with CDMOs start too late. To avoid any risk of delays, it is advisable to start discussions with CDMOs at least 18–24 months before the planned study date.

PHASES II AND III

In phases II and III, the development program will differ a lot depending on the indication and regulatory strategy. Number of patients, study length, comparators etc. will all vary. Often this phase lasts for several years. Any delay will mean a later launch date and postponed revenues. The most common source of delays is that patient recruitment to the studies is too slow and it is vital that the clinical research organisation (CRO) has a realistic plan for this. It is also important to plan the CTM thoroughly in case there are deviations from the original timeline. For instance, the shelf life of the CTM may expire if there are delays due to slow recruitment.

The manufacturing processes and control methods need to be developed so that they are fit for the final commercial product. There are several areas apart from safety and efficacy that are of importance, in particular: shelf life, convenience for the patient (and healthcare professionals for hospital care products) and suitability for large-scale manufacturing.

A long shelf life is important for both optimal product use and profitability. Usually, at least 36 months in room temperature is desired. The shelf life depends on the physical and chemical stability of the product. Poor stability is a common challenge in formulation development and it needs to be addressed as early as possible. By using accelerated stability studies (applying elevated temperature and/or high humidity) stability issues can, in many cases, be detected and addressed in a few months. However, real time studies must also be performed. To study stability, analytical methods that are stability indicating are needed. In general degradation is too small to be detected by analysing the active ingredient. Instead methods that can detect degradation products are needed.

Convenience is not of huge importance in phase I when healthy volunteers are taking the medication just a few times. However, convenience is crucial for patients that use these products on a daily basis, such as bad taste, swallowing large tablets, painful injections, or badly smelling creams. Modified release preparations that allow daily administration instead of several doses per day, as well as limiting adverse effects, may boost convenience. Fixed dose combinations are making administration easier for patients that are taking many different drugs.

Suitability for large-scale manufacturing requires the appropriate selection of raw materials, equipment and processes. In particular, all processes need to be robust and scalable. Furthermore, the analytical control methods must be suitable for routine use. Here it is of tremendous value if the development scientists are experienced in collaborating closely with full-scale manufacturing. In general, the product should be final by the start of phase III to avoid costly bridging studies.

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TECH TRANSFER

In most cases, it is recommended that production is transferred to the commercial manufacturing site before the start of phase III. By doing so, you can ensure that the CTM used in the pivotal clinical studies will have identical properties to the material that will be sold after launch. A successful tech transfer is started early in the development work. Selecting processes and equipment that are available and work well in a large-scale commercial manufacturing setting is vital. The easiest way to ensure a smooth tech transfer is probably to contract the same CDMO for both product development and manufacture, which will reduce the risk of problems and clarifies responsibility if there are any issues.

An important tool to ensure robust manufacturing methods as well as quality control is validation. Analytical chemistry methods can either be validated at the development site and then transferred to the manufacturing site or validated directly at the manufacturing site. Manufacturing methods are always validated at the manufacturing site, usually by manufacturing three consecutive batches with a successful outcome.

REGULATORY APPROVAL AND LAUNCH

Putting together the registration dossier is usually a hectic phase of a development project. Various documents have to be compiled in a short time and it must all be correct. For this reason, it is vital that enough time is planned for compiling all documentation as well as to answer the questions from the authorities after submission.

As mentioned, a regulatory strategy should be available from the start of the project. It must also be updated at regular intervals. This makes it possible to start compiling some of the information for the file early on.

In order to ensure that the questions from the regulatory authority can be answered in a timely manner, it is important to prepare for questions than can be anticipated and plan to have experts available to answer unexpected questions.

FINALLY

A drug development project is performed over several years and involves many different experts. Close collaboration is vital if the time plan is to be met, even despite unavoidable, unforeseen issues. Doing this is challenging even in large companies that can rely on in-house expertise. For a small organisation, it is vital to choose the right partners, plan carefully and ensure effective communication. The project manager has a vital role in ensuring this.

Through careful planning, many problems can be avoided but a drug development project without unforeseen issues is not very likely. In fact, one of the most important attributes of a successful drug development team is the ability to solve unexpected problems efficiently. In addition to good communication and project management, technical skill and a “can-do” attitude is essential.

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10 RULES FOR SUCCESSFUL PHARMACEUTICAL DEVELOPMENT:

1. There are no problem free development projects but you can decrease the risk of problems by working with experienced people and performing a careful risk analysis.
2. Know where you want to go from the start. Define a target product profile and a regulatory strategy before starting development.
3. Order enough GMP API. API is expensive but it is even more costly to be delayed due to lack of API.
4. Careful coordination will help to avoid delays. API manufacture, formulation development, stability studies, clinical trial material manufacture, clinical study, bioanalysis etc. are interdependent activities. It is important to consider how they can be best coordinated, especially if multiple service providers are involved.
5. Do not underestimate the importance of the dosage form and the package. The API is just a part of the product. Dosage form and package can improve efficacy and profitability.
6. Analytical chemistry is half the development. Without excellent analytical chemists working in close collaboration with the rest of the team you are likely to fail.
7. Plan for clinical trials in good time. Expect at least 12 months for the development and manufacture of drug product for a clinical trial and 6–12 months for the manufacture of GMP API. Discuss with the clinical experts and define dosage form, dose, number of doses, package, length of study and if a placebo is needed early on.
8. Your methods must be scalable. Manufacturing and control methods must work at the manufacturing site. Make sure that you involve manufacturing experts early on.
9. Close communication within the project group is vital. Deviations from the plan will occur. It is important to be able to deal with these rapidly.
10. Make sure you have a lot of enthusiasm in the team and a steady supply of coffee.

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ABOUT RECIPHARM

Recipharm is a leading contract development and manufacturing organisation (CDMO) headquartered in Stockholm, Sweden. We operate development and manufacturing facilities in France, Germany, India, Israel, Italy, Portugal, Spain, Sweden, the UK and the US and are continuing to grow and expand our offering for our customers.

Employing around 9,000 people, we are focused on supporting pharmaceutical companies with our full service offering, taking products from early development through to commercial production. For over 25 years we have been there for our clients throughout the entire product lifecycle, providing pharmaceutical expertise and managing complexity, time and time again. Despite our growing global footprint, we conduct our business as we always have and continue to deliver value for money with each customer's needs firmly at the heart of all that we do. That's the Recipharm way.

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