

1

Drug Life Cycle

1.1 Introduction

A drug life cycle is a succession of activities that starts with a research project in which new drug molecules are either discovered in nature or (semi-)synthesised or designed *de novo* in medicinal chemistry laboratories and ends when the drug is removed from the market. The process of drug discovery and design is characterised by intense intellectual creativity and biological and molecular exploration, by trial and error approaches and by frequent and recurring data collection and interpretation. Its course is largely dependent on the approaches taken by individual scientists. Once a molecule with promising characteristics is identified, it is developed into a drug product during a process known as ‘drug development’. The objective of drug development is to bring safe and effective drugs to the patient. Drug development is a highly structured process that is conducted in a stepwise fashion that is also referred to as a ‘stage gate process’ or a ‘phased review process’ whereby chemical, pharmaceutical, nonclinical and clinical information is gathered, critically reviewed and assessed before a new phase of development can proceed. While the discovery of a new drug molecule is characterised by a high degree of freedom, the process of drug development is highly structured. This is due to regulations imposed upon the process by health authorities such as the US Food and Drug Administration (US FDA) and the European Medicines Agency (EMA). Every step of the process is carefully timed and linked to the previous step and the next step. It is a process that is well planned and controlled. Drug development is complex and it is characterised by failures, reiterations and reassessments of scientific data and by intensive interaction among different scientific disciplines. It is not a matter of pharmacology or medicine alone but it also involves chemical engineering, process chemistry,

Global New Drug Development: An Introduction, First Edition.

Jan A. Rosier, Mark A. Martens and Josse R. Thomas.

© 2014 John Wiley & Sons, Ltd. Published 2014 by John Wiley & Sons, Ltd.

manufacturing plant management, biostatistics, drug-delivery sciences, bio-pharmacy, materials sciences, physical chemistry, medicinal chemistry, and supply management all working together in harmony with disciplines such as pharmacology, clinical research, clinical data management, bioinformatics, bio-analytical chemistry, pharmacokinetics, toxicology and other scientific disciplines in the life sciences. On top of the challenge of making these different disciplines work together, there is the continuous uncertainty as to whether the drug candidate, at the end of a drug development process of about 6-10 years, will be demonstrated to be effective and safe in the targeted patient population. This means that the development of a new drug is a process of high risk, takes many years, requires a talented group of scientists, engineers and clinicians, consumes considerable human and financial resources and requires strong management to be successful. At the end of a development project when all scientific and medical data have become available, the quality, safety and efficacy are critically reviewed by the health authorities. The new drug will only be approved when they are convinced that the drug complies with the criteria of quality, safety and efficacy, and has a positive benefit–risk balance. As a result, the drug development organisation will receive a marketing authorisation and is allowed to put the drug on the market.

The new drug may remain on the marketplace for a considerable amount of time and new research can be initiated to show that the drug can be used for other therapeutic indications, be administered via other routes of administration or combined with other drugs. A drug, however, has a limited ‘lifetime’ on the market and at one point in time the decision can be taken to withdraw it from the market. Such a decision may be based on the entry of new and better drugs on the marketplace or expiry of the patent life with competition from less-expensive generic drugs as a result. Alternatively, a drug may be withdrawn from the market because it has been shown to have unacceptable side effects. This process of post-approval activities is the last and major step in the process of a drug life cycle.

1.2 Drivers of the search for a new drug

Before embarking on the search for a new drug, the R&D organisation, which can be a private company or a non-for-profit organisation, has to decide whether it is worthwhile to engage in an expensive and risky drug R&D project. According to Hill & Rang [1], the following criteria are to be considered before such a decision is taken:

- I. Strategic considerations that address the question whether the R&D organisation should embark on the drug R&D project at all (should it be done?).

- II. Scientific and technical considerations that address the question whether the project is technically feasible (can it be done?).
- III. Operational considerations that address the question whether the project – if feasible – can be conducted within the boundaries of the organisation. In other words, whether the organisation has the required organisational, infrastructural, human and financial resources (can we do it?).

1.2.1 Strategic criteria

By far the most important selection criterion is whether the new drug – if developed – will meet an unmet medical need. An area of unmet medical need is a therapeutic area in which there is an absence or lack of safe and effective drugs and where the introduction of a new drug can offer benefit to patients. Strategic considerations require a thorough analysis of the epidemiology of the disease, its current pharmacotherapy and projected pharmacotherapy at the time when the new drug will be available, i.e. after approx. 7 to 12 years. The gap between what is achievable and what is desirable is analysed and a decision is made whether it is worthwhile to fill this gap. It can be large (e.g. there is no good drug available nor in development at this moment) or it can be small (e.g. there is a need for a better pharmaceutical dosage form that reduces the side effects or leads to more comfort for the patient than the current drug on the market). Unmet medical need is one of the factors affecting the future market potential of a new drug, i.e. whether the project can generate return on investment (ROI), but there are many others, to name a few: predictions of disease prevalence and incidence, acute versus chronic diseases, market share of competitors, drug regulatory hurdles, drug reimbursement policy, future patent cliffs, etc. Other strategic factors are related to the company or organisation wishing to search for the new drug, e.g. the therapeutic areas and markets a company is well established in, the focus on small molecules versus biotech products, the current and future state of the drug pipeline, the willingness to play in the blockbuster league or to focus on niches, the financial health of the company, etc.

1.2.2 Scientific and technical criteria

A drug development project should be technically feasible. It is important to consider whether the drug development ‘idea’ can be transformed into a scientific hypothesis that can be tested in a clinical environment. For example, although the development of drugs for AIDS prevention may be worthwhile, the translation of a scientific hypothesis (‘drug X will prevent the occurrence of AIDS in a specific group of individuals’) into a development plan may be very challenging if not impossible to complete because of the recruitment

of volunteers for the clinical trial, the time it may take to (dis)prove the hypothesis and the ethical impact of the clinical exploration. Alternatively, the availability of a technological platform for the development of a complex dosage form such as an implant, may drive the decision to proceed. The feasibility of a project can also be hampered by projected difficulties, especially during clinical development, safety evaluation or pharmaceutical formulation research. Drugs against chronic diseases may require a much larger investment in long and expensive clinical trials than drugs to treat acute diseases. On the one hand, drugs that are developed to treat 'lifestyle diseases' such as diabetes type 2 and obesity should be very safe to use and require a considerable safety investigation before market authorisation is granted. On the other hand, drugs to treat life-threatening diseases such as cancer may show side effects that non-cancer patients would and should not tolerate. Developing a new drug can be worthwhile when a competitive advantage can be expected. This is certainly true for a 'first-in-class' drug (the innovator drug in a new therapeutic class), but also for a 'fast-follower' drug (the 2nd or 3rd one in a new class, but better than the innovator) and a 'best-in-class' drug (aiming to be the best one). These are very ambitious R&D programmes that require considerable investments when compared with the investment required for 'me too' ('I can do as well') or 'me better' ('I can do somewhat better') drugs that are easier to develop. However, 'me too' or 'me better' drugs can sometimes successfully complement a well-balanced innovative drug portfolio. Another important scientific factor is the potential to protect the intellectual property of the new drug by means of a patent, giving the owner the exclusive right to commercialise the drug for a given period of time (usually 20 years from the date of filing) which can be extended under certain conditions. The period that the drug is protected by a patent once on the marketplace is short because R&D takes a considerable amount of time. This period is important for the pharmaceutical industry to allow a return on R&D investment before generic (or biosimilars in case of biotech drugs) enter the market once the patent expires.

1.2.3 Operational criteria

A key operational criterion for the choice of a drug development project is the comparison of the required resources with the available resources. This includes the availability of staff and expertise, as well as facilities, equipment, materials and capital. Not every activity in drug R&D has to take place within the drug R&D organisation, but every activity that is outsourced has to be financed. The timescale for a complete drug R&D cycle is another important factor. Some drugs can be developed in a – relatively – short period of time such as drugs to treat acute infections, or can even be 'fast tracked' when the

medical need is high, while other drugs may require many years to develop such as drugs against osteoporosis. Longer development times increase the cost and reduce the time for patent protection during commercialisation. If a company finds ways to develop drugs faster than its competitors, this ‘time crunching’ capacity can be an important driver for the development of a new drug.

The decision to start the search for a new drug will depend on the careful consideration of all the criteria mentioned above. The overall analysis is usually performed by operational people taking into account the strengths and weaknesses of the new drug and the drug development organisation versus the opportunities and threats in the environment and the marketplace (SWOT analysis) to name the simplest approach.

1.3 Structure of a drug life cycle

The life cycle of a drug involves four consecutive phases: drug discovery and design, drug development, regulatory review and approval, and commercialisation and marketing.

Drug discovery and design consists of an exploration phase, an assay development phase, a screening phase, a hit-to-lead phase and a lead optimisation phase. There are many sources of new drug molecules: natural sources such as micro-organisms, plants or animals or libraries of drug molecules that either have failed or have been used for other therapeutic areas. These molecules can be structurally modified and be subjected to pharmacological screening tests. Drug molecules can be modified to improve their pharmacological activity and bioavailability and to reduce toxicity before they are ready for transfer to drug development. This is described in more detail in Chapter 2. A drug molecule that is selected for development is referred to in this book as a ‘drug candidate’.

Drug development can be subdivided into two major phases: early development and late development. Early development has a pre-clinical and a clinical phase whereas late development has a pre-approval and a post-approval phase. During early development the drug candidate is carefully studied with the objective to prove that its properties can justify its introduction into a late development programme. An essential principle of early development is the ‘Proof-of-Concept’, which means that it can be proven that the molecule does what it is purported to do in a small group of patients under well-controlled conditions. The objective of the late development part of a drug development project is to confirm that the claims of the therapeutic use in a small group of patients can be justified in large clinical trials with a large number of patients suffering from the disease the molecule is intended to treat. A candidate drug

that has transferred from early development to late development is referred to in this book as a ‘drug under development’.

When the final results of drug development show that the drug under development is safe and effective and can be manufactured at a high level of quality, all the data are collected, integrated and submitted to the health authorities in order to obtain authorisation for marketing. The regulatory approval process takes a considerable amount of time because the authorities responsible for granting marketing authorisation need time to carefully assess the therapeutic value and the safety of the new drug.

Once market authorisation is granted on the basis of a positive benefit–risk balance, the drug can be introduced (‘launched’) into the market. From this point in time pharmaceutical marketing further drives the life cycle of the drug. It takes approximately 7–12 years from the identification of a drug target in the human body to the introduction of a new drug into the market. While on the market, efforts in drug development continue to refine the manufacturing process, to improve pharmaceutical formulations and to explore new routes of administration or new therapeutic indications. During the market life of a new drug its use is continuously monitored to detect side effects to improve its safe use in clinical practice. At the end of the drug life cycle the drug can be withdrawn from the market place for various reasons. It can either be because of safety reasons, expiry of patent life or because of replacement by a superior drug of the same class. An overview of the drug life cycle is given in Figure 1.1.

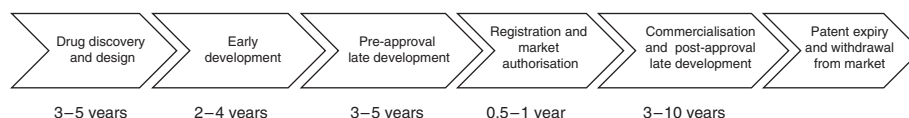


Figure 1.1 The drug life cycle.

1.4 Costs and risks of drug research and development

1.4.1 Cost drivers

The cost of drug R&D is considerable and is primarily driven by clinical (approx. 60% of total cost) and chemical and pharmaceutical R&D (approx. 30% of total cost). Another cost driver is the large number of studies in experimental animals required to demonstrate the nonclinical safety and efficacy of the drug. In addition, the synthesis of a new drug can be a complex undertaking that requires important investments in manufacturing

plant infrastructure, equipment, chemicals and pharmaceutical drug-delivery technologies.

1.4.2 Estimates of drug development costs

It is generally accepted that the cost of a drug development project ranges from 800 million USD to approximately 1 billion USD [2, 3, 4, 5]. These figures are frequently mentioned in the literature and the lay press but have been subject to criticism because scholars observed that drug development costs are highly variable or unknown [6, 7]. For example, tax savings are not taken into account, clinical trial costs are inflated and development times are exaggerated. Alternative calculations led to drug development cost predictions ranging between 180 and 231 million USD. Still others have projected drug development costs to range between 500 million USD and more than 2 billion USD [3]. However, it is a fact that the investment required to discover and develop a new drug is substantial and involves considerable risk since it is only known at the end of late drug development whether the drug is or is not effective and safe in patients and can be put on the market.

1.5 Risks of drug R&D

There are two kinds of risk in drug R&D: therapeutic area/portfolio risk and project risk.

Therapeutic area/portfolio risk is associated with the choice of the therapeutic area in which a drug R&D organisation intends to develop new drugs. When a drug company makes the strategic decision to move into a new therapeutic area there is always the risk that no molecules can be discovered and/or designed that have a promising therapeutic activity or that even an interesting active molecule cannot be developed into a new medicinal product. Project risk is related to a given drug R&D project. This is discussed in more detail in Chapter 3.

1.5.1 Failure and success rates in drug development

The failure rate of new drug candidates to make it through the development process is called attrition. An attrition of $x\%$ means that $x\%$ of the projects has been terminated during a given phase in drug development or in drug development as a whole. High attrition means that the number of drug candidates that are introduced into the drug pipeline substantially drops during the different development phases. Zero attrition – a theoretical concept – means that all drug candidates that enter the development pipeline make it to an approved drug and are launched in the market. Attrition rates are important

to management since it is an indicator of the productivity and efficiency of the drug R&D organisation. The average success rate for all therapeutic areas is approximately 11% [8]. Success rates differ according to the therapeutic area and range from 5% for oncology drugs to 20% for cardiovascular drugs. Even if a drug candidate eventually makes it through development, it is still not certain whether the application for market authorisation will be approved by the regulatory authorities. The failure rate during regulatory review by the authorities is 25%. In the case of oncology products the failure rate is as high as 30% [8]. This high failure rate may impact the potential survival of a drug company since at this stage all financial resources have been consumed and costs incurred. For small companies that have invested all their resources in a single drug, a refusal for market authorisation may result in the death of the company. The failure to bring one drug on the market can be absorbed by R&D firms with a large and diverse product portfolio but many consecutive failures may have dramatic consequences.

Although attrition is generally referred to as the failure rate for a drug development portfolio in one or more therapeutic areas, it can also be used to determine the failure rate for each phase of the drug development process. In other words, it can be determined for each transition of a drug candidate from early to late development or from marketing authorisation to approval. Approximately 60% of all the drug candidates that are tested for the first time in man (Phase 1 clinical trials) are approved for testing in exploratory pharmacology trials in patients (Phase 2 clinical trials) and approximately 20% are admitted to confirmatory pharmacology trials (Phase 3 clinical trials). Only about 10% of all drug candidates that are admitted to testing in humans make it to the marketplace. The most important reasons for attrition are efficacy, toxicity and commercial [8]. If one were able to increase the probability of technical success by decreasing attrition either for the total project or for each phase of development, productivity would increase accordingly. A detailed discussion on the possible approaches that can be used to increase R&D productivity of new drugs is beyond the scope of this book but can be found in several scholarly papers and books that address this topic [9–17].

1.5.2 Net present value

A portfolio is a collection of drug products in R&D and on the marketplace. Defining which drug development project and therapeutic areas will constitute a portfolio is a difficult task and is associated with a risk that is referred to as 'portfolio risk'. It is a strategic decision that is taken by top R&D management. For example, the decision to switch from a cardiovascular-based R&D portfolio to an ophthalmology-based R&D portfolio involves a myriad of separate decisions that involve experts from basic research, medicinal chemistry, market analysis, finance, drug development and regulatory affairs. One of the

most straightforward methods to value a project is to estimate the financial benefits from it and subtract the costs to give a net value. This rather simple deduction can be sophisticated by bringing in the time-related value of money as income today is worth more than income next year and early expenditure is more costly than later expenditure. This leads to a figure called the Net Present Value (NPV) that evaluates the financial impact of a new drug R&D project and is helpful in taking strategic decisions [18]. It goes beyond the scope of this book to enter into a detailed discussion of the value of NPV but suffice it to state that projects with a negative NPV should be abandoned, while projects with a positive NPV may be considered for inclusion in the portfolio. Although the NPV calculation allows the assessment of a project on a purely financial basis, it is not, and should not be, the final answer to the question of project selection. What is required more than the financial expertise needed to perform NPV calculations is the intimate knowledge of the medical need that drives the development of a new drug. It is therefore not surprising that some drugs with a low NPV were developed and became drugs that generated considerable income for the company and benefit for the patients. The success of a new drug is therefore not always driven by financial parameters alone.

1.6 Value for patient and society

The selection of a drug development project should not only be based on NPV and shareholder return. More importantly, there should also be a return to society at large. Gradually, drug R&D companies realise that their long-term future will not only be driven by financial success but also by the realisation that they should contribute to society and provide answers to medical needs. Some major organisations have started the development of drugs for small markets with high medical need realising that the financial returns would hardly compensate the investments made. Although there are only a few of these projects it shows that the trend for contributing to society and to patients is steadily – albeit slowly – finding its place next to shareholder value contribution. Alternative approaches have been introduced such as the Health Impact Fund [17].

1.7 The end of a drug's life

Most withdrawal decisions are either driven by a substantial drop in sales or safety concerns. For example, drugs such as cisapride, grepafloxacin and terfenadine were removed from the market because of cardiovascular side effects and bromfenac and troglitazone because of hepatotoxicity. They have been on the market for only a relatively short period of time. Other drugs are removed

from the market for reasons of competition because more innovative and better drugs reached the market and make the use of the original drug obsolete. Alternatively, when the end of its patent life is reached, the original drug is pushed out of the market by 'generic' drugs. Generic drugs are copies of the original drugs developed by the R&D drug industry and can be introduced in the market after it is shown that they are bioequivalent with the original drug.

1.8 Management

The development of a new drug requires a sound scientific strategy, clear planning, careful financial control, flawless execution and a correct decision-making process. Above all, it requires scientists, engineers and clinicians who are not only experts in their field, but who are also capable of understanding the other scientific disciplines sufficiently well to appreciate their impact on their own field and the fields of others involved in the project. Because of the high failure rate in new drug development they should also have a strong personal conviction about the added value of their work and the contribution they may bring to patients and society. This means that the development of a new drug is not only time consuming and expensive but also requires strong management and leadership in order to reach development milestones on time, to control budgets, to evaluate investments and to manage human resources.

In general, this process is led by a portfolio team that manages the drug portfolio of a company, while project teams manage the process of discovery and development. A portfolio team operates at the level of top management and addresses strategic questions regarding the drugs to be developed or which therapeutic area to be targeted. Once the decision is taken to start the discovery and development of a new drug in a specific therapeutic area, a project team is established that conducts the discovery project with the objective to identify a new molecule from which a new medicinal product can be developed. The drug discovery process is discussed in more detail in Chapter 2.

References

- [1] Hill RG, Rang HP. (2013) Drug discovery and development. *Technology in transition*, 2nd edn, Churchill Livingstone/Elsevier, Edinburgh.
- [2] Dimasi JA, Hansen RW, Grabowski HG. (2003) The price of innovation: new estimates of drug development costs, *Journal of Health Economics* **22**, 151–185.
- [3] Adams CP, Van Branter V. (2006) Estimating the cost of new drug development: Is it really \$802 million? *Health Affairs* **25**, 420–428.
- [4] Anonymous. (2003) New estimates of drug development costs (Editorial). *Journal of Health Economics* **22**, 325–330.
- [5] Anonymous. (2003) Costing drug development (Editorial). *Nature Reviews Drug Discovery* **2**, 247.
- [6] Light DW, Warburton R. (2011) Demythologizing the high cost of pharmaceutical research, *Biosocieties* 1–17.

REFERENCES

11

- [7] Angell M. (2005) *The truth about drug companies: How they deceive us and what to do about it*. Random House, New York.
- [8] Kola I, Landis J. (2004) Can the pharmaceutical industry reduce attrition rates? *Nature Reviews Drug Discovery* **4**, 711–715.
- [9] Kola I. (2008) The state of innovation in drug development. *Clinical Pharmacotherapy & Therapy* **83**, 227–230.
- [10] Booth B, Zemmil R. (2004) Prospects for productivity. *Nature Reviews Drug Discovery* **3**, 451–456.
- [11] Garnier J. (2008) Rebuilding the R&D engine in big Pharma. *Harvard Business Review* **86**, 68–76.
- [12] Paul SM, Mytelka DS, Dunwiddle *et al.* (2010) How to improve R&D productivity: the pharmaceutical industry's grand challenge. *Nature Reviews Drug Discovery* **9**, 203–214.
- [13] Scanell JW, Blanckley A, Boldon H *et al.* (2012) Diagnosing the decline in pharmaceutical R&D efficiency. *Nature Reviews Drug Discovery* **11**, 191–200.
- [14] Sams-Dodd F. (2005) Target-based drug discovery: is something wrong? *Drug Discovery Today: Targets* **10**, 139–147.
- [15] Pandey M. (2003) Investment decisions in pharmaceutical R&D projects. *Drug Discovery Today* **8**, 968–971.
- [16] Pritchard JF, Jurima-Romet M, Reimer MLJ *et al.* (2003) Making better drugs: decision-gates in non-clinical drug development. *Nature Reviews Drug Discovery* **2**, 542–552.
- [17] Pogge T. (2010) The Health Impact Fund: Better Pharmaceutical Innovations at Much Lower Prices. In: Pogge T, Rimmer M, Rubenstein K (eds.) *Incentives for Global Health: Patent Law and Access to Essential Medicines*, Cambridge University Press, Cambridge.
- [18] Goffin K and Mitchell R. (2010) *Innovation Management Strategy and Implementation using the Pentathlon Framework*, Palgrave Macmillan, New York.

