The process of drug development from the laboratory bench to the market

In this month’s science article, Timothy J. Snape and Alison M. Astles discuss the processes involved in drug discovery and the methods used in developing new drugs from the laboratory bench to the market place.

Finding a blockbuster drug with sales in excess of £1bn has been likened to finding a needle in a haystack. Many of us are aware of the prolonged and expensive delivery times for new medicines to progress from the laboratory bench to marketed products but, with the added hurdle of National Institute for Health and Clinical Excellence approval processes in England and Wales, getting a drug to market can be a tough journey. Knowledge of the rigorous process for drug development, and of the occasional dramatic failures, helps us, as healthcare professionals, understand why the market for medicines looks as it does. Likewise, our role in supporting adverse drug reaction reporting is vital for maintaining medicines safety. In a complex international marketplace, the underpinning sciences of chemistry, pharmacology and pharmaceutics are as important as ever.

This article aims to summarise the main areas of drug discovery and draw attention to the huge amount of scientific effort that goes into the production and development of modern medicines before they reach the market place. In essence, we wish to revisit the campaign launched by the Royal Pharmaceutical Society back in April 2000, which emphasised that “medicines don’t just happen”.

For pharmaceutical companies, there are economic factors as well as medical ones that need to be satisfied in order to offset the huge costs implicated with designing a new drug and seeing it through to the market place. Any new drug research programme will need to ensure that the potential financial returns are worth this huge investment.

Once the disease has been agreed on, the drug’s target needs to be identified. This may be a specific receptor, enzyme or other protein, nucleic acid or cell membrane that is implicated in some way in the disease state, and the research team will need to identify any potential targets before deciding whether the drug to be developed will, for example, activate or deactivate a particular receptor or inhibit a specific enzyme. At this point, pharmacology is brought into play. It sets out to find suitable screening methods and to develop suitable activity and toxicity assays.

Finding a lead compound

Once all this has been established, the next hurdle is to find a lead compound that shows the desired pharmacological activity. This initial compound may not be very active or may have undesired side effects. However, it provides a starting point for drug design and optimisation. There are a number of sources from which the initial lead compound can be found, and the more common ones are discussed below.

Natural products The chemical structures of many of today’s drugs have been inspired by the complexity of natural products or have been developed from lead compounds that were originally developed from a natural product. Key pharmacy examples that have used this approach to market include: rosuvastatin and other statins, which were developed from a lead compound produced by the micro-organism *Penicillium citrinum*; and captopril and other angiotensin-converting enzyme inhibitors, which were inspired by the action of snake venom.

Moreover, natural products themselves may be used as drugs (eg, morphine, paclitaxel and vancomycin).

Synthetic compound libraries During the course of drug development, pharmaceutical companies store thousands of small molecular building blocks and other drug-like molecules, which they can screen against any biological target for potential hits, regardless of what the compound may have originally been made for. Similarly, pharmaceutical companies can buy such compound libraries from other sources for the purposes of screening and finding a new lead compound. It is only once a “hit” has been found that traditional drug development and optimisation can start, and many of today’s drugs are developed from such starting points.

Existing (“me-too”) drugs Over the course of a drug’s lifetime, provided it has been on the market long enough, its weaknesses will have been noted, allowing other pharmaceutical companies to target this class in the hope of developing a better drug. One only has to look at the penicillin class to see the improvements that have been made with
modern penicillins (improved selectivity, better potency and stability) when compared with the original compounds.

Similarly, the original manufacturer of the drug may choose to develop new salt forms and different formulations of the drug to improve it, e.g., for oral absorption or for better therapeutic efficacy. Follow-up compounds may also be developed from analogues, e.g., a sulphonamide antibacterial agent; tipranavir, a more selective HIV protease inhibitor; or felodipine, a calcium channel blocker.

**Side effects**
The undesired side effect of one drug could, if enhanced and exploited properly, be the starting point for the development of a new drug for a different therapeutic area. The goal for a medicinal chemist would then be to “undesign” the major biological activity of the drug by changing its chemical structure appropriately while maintaining and enhancing the previously undesired activity. Several drugs on the market have followed this principle, notably: tolbutamide, which was developed through the exploitation of the hypoglycaemic side effect of a sulphonamide antibacterial agent; trpanavir, an antiviral, which was developed by the optimisation of a side effect of warfarin; cimetidine, which is an antacid, but by noting that it helped patients give up smoking, is now marketed for smoking cessation; and not forgetting the well known example of Viagra’s (sildenafil citrate) discovery.

**Target’s natural ligand**
By definition, the natural ligand is already able to bind to the target of interest but, usually, it requires structural optimisation if it is to become a drug available on prescription. Examples that have followed this route to market include salbutamol, which was developed from the natural bronchodilator adrenaline, but was further optimised to eliminate the undesired stimulation of the heart and elevation of blood pressure associated with it, ultimately resulting in a drug capable of selectively relaxing bronchial muscle. Also, cimetidine and ranitidine, the H₂ histamine antagonists used for reducing gastric acid output, were developed from the natural antihistamine.

Once a lead compound has been established, medicinal chemists move forward by preparing analogues of it, which enables them to study structure-activity relationships. The purpose of such studies is to determine which parts of the molecules are important to biological activity and which are not (and to optimise those that are) in order to develop the best compounds possible, not only in terms of pharmacological activity, but also by increasing selectivity towards the target and reducing undesired side effects. This stage may also include computational modelling of the target and lead compound in order to try to improve interactions with the target through the rational design of future analogues.

During these early stages, laboratory and animal testing is carried out in order to identify the most promising lead compounds, along with elucidation of the mode of action of the drug to establish proof-of-principle, efficacy and acute and chronic toxicity. Pharmacokinetic studies also take place that establish the absorption, distribution, metabolism and excretion of the compound. At this stage, patent protection is usually acquired, along with establishing the long-term stability of the drug and the best formulation for it.

The project phases up to this point typically last about four to five years and are followed by time- and resource-demanding clinical trials, regulatory issues and marketing, which normally takes a further five to seven years.

**Clinical trials**
If the drug, up to now, has demonstrated the desired effect in animal tests, it can exhibit a distinct advantage over existing therapies, has acceptable pharmacokinetics, no serious side effects and also has a good half-life and few metabolites (a tall order indeed), then the company may decide to take the compound(s) into clinical trials. This is where clinicians will take over and the scientists are left primed to make further analogues in case one of the trial compounds fails and further work is needed before an acceptable drug is achieved. These trials include three phases before approval that need to be successfully passed before the drug can be marketed. These are:

- **Phase I clinical trials** Studies on about 10–20 healthy volunteers to establish safety, dosage, and blood levels of the best few compounds; placebo controls are in place
- **Phase II clinical trials** Studies on a few hundred patient volunteers to evaluate the drug’s effectiveness and its side effects; the short-term safety of the drug and the best dose regimen is established at this point
- **Phase III clinical trials** Studies on a few thousand patient volunteers to verify efficacy and monitor adverse long-term use; fine-tuning the dose and identifying any rare side effects and comparison to drugs currently on the market also take place.

Increasingly, NICE is becoming involved in early stage discussions with pharmaceutical companies about the design of their trials, commonly at phase II, for compounds in development that may be referred for a technology appraisal. This helps companies ensure that the clinical and cost-effectiveness data they produce will be appropriate for NICE review at a later stage. If the drug successfully passes phase III studies, it can be registered, approved and placed on the market and can be prescribed. It continues to be monitored for effectiveness and for rare or unexpected side effects. These are known as phase IV studies. The yellow card system is in place for healthcare professionals and patients to report any adverse reactions that are suspected to be related to a drug or a combination of drugs. In the case of new drugs, or other intensively monitored medicines, all suspected reactions should be reported, including those that are not considered to be serious, in order for any side effects, which may only be highlighted once the medicine is used by a much larger number of patients under the conditions of everyday use, to be seen. In addition, some side effects may not be discovered until many people have used the medicine over a period of time.

Even once a drug has been developed and approved, the story does not end. Many drugs on the market today have more than one indication (e.g., carbamazepine, aspirin and minoxidil) or are used for an uncensored indication (e.g., amitriptyline, metformin and ciclosporin), all of which may have to expand our arsenal of drugs to combat disease. Most of these additional indications will have been developed from an acutely observed side effect at the development stage or once it is established on the market.

**Summary**
This article has aimed to highlight that medicines do not just happen and that, at best, it takes many years (approximately 10–12) to introduce a new drug to the market. Such is the high attrition rate of developing new drugs that it is inevitable that most projects are terminated before marketing and even at the advanced stages of clinical studies. For example, for every 10,000 structures synthesised, 500 will reach animal testing, 10 will reach phase I clinical trials and only one will get to market, usually at a cost of approximately £444m. However, by continuing to draw on the knowledge and expertise of pharmaceutical scientists, as well as applying both new and established methods to drug development, we will undoubtedly continue to improve our chances of developing new drugs for the future.