How prescription drugs are developed

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Summary

Modern drug development is a risky business both for pharmaceutical companies and patients. Many thousands of promising compounds need to be tested. Following discovery of a promising compound, extensive animal and human trials are undertaken in consultation with government regulators under strict ethical conditions to provide evidence that the new drug works, is safe and is manufactured using the highest quality standards. This evidence is evaluated by the regulatory authorities and, if acceptable, leads to the registration of the new medicine. Once registered the new medicine may be submitted for government subsidy. In Australia, if the drug demonstrates cost-effectiveness it may become available on the Pharmaceutical Benefits Scheme.

Key words: clinical trials, drug evaluation, drug industry.

(Aust Prescr 2006;29:159–61)

Introduction

In April 2006 six healthy young male volunteers required intensive care following administration of a new experimental compound. The investigational drug TGN1412 was a monoclonal antibody specific for a membrane receptor present on the surface of white blood cells. It was developed by TeGenero, a pharmaceutical company, and had been trialled in monkeys at 500 times the dose initially administered to humans in the phase I safety trial. Despite this, a reaction occurred that had not been seen or suspected from the animal trials, and all six volunteers very nearly died. Subsequent investigations have suggested that the non-binding tail of the antibodies formed multiple cross-linkages and induced a massive flood of inflammatory mediators, referred to as a cytokine storm, resulting in an overwhelming systemic inflammatory reaction and multiple organ failure. This tragedy illustrates the hazards of drug development.

Drug development has moved from its origins of simple empiricism and serendipitous use of plant-derived alkaloids, to a highly complex systematic process. It starts with basic research, which can involve molecular biology and genetic manipulation, vast molecular libraries and automated screening, and computer-assisted drug design. From this, promising compounds are tested in animal studies before going on to human trials.

Drug discovery

In an ideal world, a new drug is discovered in a purposeful way in response to an unmet clinical need. Drugs are mainly developed by pharmaceutical companies, although the early research, which leads to identification of either a biological target such as a new cell membrane receptor, or a new compound that interacts with a biological target, may also be performed in government-funded research institutions.

Techniques such as computer-assisted drug design are employed to elucidate the three-dimensional structure of a particular biological target and to design a molecule that interacts specifically with that target. Drug researchers also have access to libraries containing large numbers of molecules which are screened against multiple *in vitro* biological targets using high-throughput computerised processes looking for a significant receptor-ligand reaction.

More recent advances in biotechnology have provided drug researchers with new biological targets such as cell membrane channels, as well as active complex biological proteins such as hormones. An example of this is the discovery that erythropoietin is a key regulator of red blood cell production. The identification of the gene encoding its amino acid sequence, and the subsequent insertion of this human gene into a non-human mammalian cell, allowed erythropoietin to be mass-produced for the treatment of anaemia in patients with renal failure.

Despite these technological advances, serendipity has been responsible for many of today's medicines. Sildenafil, for example, was initially investigated in clinical trials as a proposed anti-anginal drug, but was noted to have a particular adverse effect. This led to a re-evaluation of its development plan, and its subsequent commercialisation as an erectile dysfunction treatment.

Once a promising new compound has been identified, it needs to undergo thorough testing to ensure that it works and is safe. Usually only a handful of the thousands of compounds tested make it through this testing to be available in pharmacies as new drugs.

Animal studies

Toxicology studies in animals are conducted before a compound can be used in humans, and government medicines regulatory

agencies such as the US Food and Drug Administration (FDA) are closely consulted in the design of these trials. Usually two mammalian species are tested, such as rats and guinea pigs, using single and repeated dose administration regimens. Depending on the type of drug being tested, specific strains of purpose-bred animals are also used, such as rats with diabetes for new hypoglycaemic drugs, or guinea pigs with a predisposition to osteoarthritis for testing of non-steroidal anti-inflammatory drugs. Reproductive toxicology tests on male and female animals with dosing commencing four weeks prior to mating are conducted to determine effects on fertility in both sexes, on embryogenesis, and on fetal malformation.

Clinical trials

Once the animal studies have suggested an appropriate dose and have provided adequate evidence that the drug candidate has some efficacy and appears to be safe, human studies may be started. Clinical trials must be conducted according to Good Clinical Practice, which defines a set of very strict conditions developed by international regulatory bodies in agreement with the principles espoused in the Declaration of Helsinki. The design of these trials is determined in consultation with one of the major drug regulators such as the FDA in the USA. Classically, there are four phases of trials in the development of a new medicine.

Phase I

Phase I trials are typically conducted in healthy young male volunteers in groups of about 10–20. They are designed to assess how the drug is absorbed, distributed, metabolised and excreted by the body (that is, pharmacokinetics) and to establish the safe dose for phase II trials.

Phase II

Phase II trials are designed to examine what effect the drug has on the body (that is, pharmacodynamics) such as heart rate, blood pressure and cognitive effects, depending on the disease the drug is being developed to treat. These studies are usually conducted in 50–100 patients with the disease rather than healthy volunteers as in phase I.

In phase I and II trials a very low dose of the investigational drug is usually given to a small number of people who are then monitored closely in a purpose-designed early phase unit. An early phase unit is similar to an intensive care ward with about 10 beds, each with sophisticated monitoring and emergency treatment facilities such as electrocardiograms, electroencephalograms, blood chemistry and haematology analysers, oxygen, intravenous fluids and resuscitation equipment. These units are often located within a hospital. If the first participants show no ill effects the dose is increased in the next group. This process is repeated several times until a minimum effective and maximum tolerated dose is established. The maximum tolerated dose is reached when a specified percentage of participants experience adverse events as predefined in the study protocol.

Phase III

Phase III trials involve larger numbers of patients with a particular disease or condition and are usually randomised comparative double-blinded studies. The comparator is either placebo or an active drug already well established as treatment for the disease under investigation, or both. Typically, several hundred patients are exposed to the investigational drug in these trials, which are designed to show efficacy and safety and to better determine the appropriate dose range. The cost-effectiveness of a drug is sometimes analysed during the phase III trial stage. In a typical development program for a new medicine, several phase III trials are required by the regulatory authorities. Unfortunately, even with a large-scale phase III program, uncommon adverse events may not be detected until the new medicine is used widely in the community. As a rule of thumb, you need to expose about three times as many patients to a drug to reliably detect an adverse event that has a particular incidence; for example, to detect a 1 in 1000 event, 3000 patients need to be exposed.

Phase IV

Phase IV (post-registration) trials are those undertaken after the new medicine has been registered and are usually randomised controlled trials. They are designed to answer important questions which help determine its clinical position (for example first-, second-, or third-line use), cost-effectiveness, and safety profile in certain patient populations.

Phase IV trials may be very large studies involving thousands of patients for several years. They are very expensive but often more useful than the earlier registration studies because they allow broader, more realistic patient groups to be studied.

Publication of study results

Timely publication of study results is critically important to allow free and rapid dissemination of new research. However, studies with negative or unfavourable outcomes are sometimes not submitted for publication, a practice frowned upon by industry, clinicians and academia. Acceptance of a proposed publication by a medical journal is dependent on many factors such as its accuracy and quality, as well as its relevance and interest to readers. Failings in any of these areas may mean a study is not published.

The pharmaceutical industry has adopted a global standard proposed by the International Committee of Medical Journal Editors whereby a study must be registered on a public website (such as the FDA's www.ClinicalTrials.gov, or the National Health and Medical Research Council's www.actr.org.au) before

the enrolment of the first patient, if it is to be published in any of the major medical journals.[1] This allows doctors and patients to easily see what studies are being conducted with particular drugs for any given therapeutic area or disease state.

Drug approval and commercialisation

Once the phase I to III program is complete the pharmaceutical company sponsor compiles all the data about the new medicine which are then assessed by the government regulatory authorities (such as the FDA in the USA, the Therapeutic Goods Administration (TGA) in Australia and Medsafe in New Zealand). The regulators examine the evidence relating to the chemistry and manufacture of the new drug, the animal toxicology, and the clinical studies. They specifically evaluate the methodological quality of the trials, as well as the efficacy and safety of the drug (the first three 'hurdles'). A new medicine must have an acceptable benefit:harm ratio in a well-defined patient group to allow it to be registered for that specific indication. Once the regulator has approved the new medicine, which can take around 14 months in Australia, the sponsoring pharmaceutical company can begin to sell and promote it.

In Australia, and increasingly in other countries, a 'fourth hurdle' for wider public access to new drugs exists – demonstration of cost-effectiveness relative to current management. After registration by the TGA, a pharmaceutical company can apply to have the drug considered for government subsidy under the Pharmaceutical Benefits Scheme. This will only be granted if the sponsor company can show that the new medicine is cost-effective compared to currently used medicines.

Conclusion

Drug discovery, development and commercialisation is a long, expensive and risky process both for the sponsoring company and the trial participants involved. For each successful entrant to the market, thousands of compounds fail to survive the testing and regulatory review process, however, the rewards for successful innovation can be substantial.

Reference

1. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. Med J Aust 2004;181:293-4.

Further reading

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Dr Barnes is the local medical director for a pharmaceutical company, Janssen-Cilag. He has also worked full-time in the past for Bayer and Pfizer, and has provided consulting services to several biotechnology companies, contract research organisations, and the National Prescribing Service.

Self-test questions

The following statements are either true or false (answers on page 171)

7. Phase I trials are usually conducted in healthy volunteers.
8. Uncommon adverse events are mainly identified before a drug is approved.

'Guiding principles for medication management in the community'

The Australian Pharmaceutical Advisory Council has published new guidelines for the management of medicines for people who follow complex medication regimes in their own homes. Launched in August 2006, the 'Guiding principles for medication management in the community' will be of benefit for older people with complex medication management. The guidelines recognise the importance of partnerships between a variety of health and community care providers. An electronic version of the principles is at http://www.health.gov.au/internet/wcms/publishing.nsf/content/nmp-guiding. The paper version of the book can be ordered from the online address or from (02) 6289 7753.