The development of *medicines*

HOW MEDICINES ARE DEVELOPED

Developing a new medicine takes on average ten to twelve years and costs more than £550 million. Before it is authorised for use by patients, it has to undergo a long and complex process of selection, testing and development.

- Around two-thirds of all medicines research in the UK is carried out by the pharmaceutical industry, which invests £10 million a day in research and development.
- The industry in the UK is among the most successful sources of new medicines in the world – a quarter of the world's top 100 medicines are British discoveries.
- Before they are authorised for general use, all medicines have to demonstrate that they are effective and as safe as possible.
- The authorisation process in the UK for new medicines is among the most efficient and closely regulated in the world.
- Rare side effects may only be identified once a medicine has been in use by many thousands of patients. There are comprehensive procedures in place to ensure that such events are monitored and appropriate warnings are issued if necessary.
- The introduction of modern treatments for a range of conditions such as AIDS, cancer and heart disease are major advances in areas of healthcare where there was previously little or no hope of long-term survival.

THE EARLY DEVELOPMENT PROCESS

New medicines are selected from many thousands of substances with the potential to treat the target condition. In the end, only a very few make it through the rigorous testing process and are eventually authorised for wider use in patients.

In the past, a chemist might have been able to produce between 50 and 100 new chemical compounds in a year. Using new techniques that use computer-controlled robots, these numbers can now be increased to nearly half a million in a week.

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High-throughput screening enables promising compounds to be selected for targets that are specific to a disease, gradually narrowing them down to the compounds that show most promise. This technique makes it possible to screen more than a million compounds against a single target in a few weeks.

Advances in **genomics** have formed a major part of the pharmaceutical industry's search for new medicines. It is now recognised that many diseases can be linked to genetics, both in terms of traits that we have inherited or of our response to environmental influences. The information gathered through the successful mapping and sequencing of the human genome is playing a vital role in the discovery process, helping to identify areas for further scientific exploration and potentially allowing medicines to be customised to groups of people or even individuals. Pharmacogenetics can help to identify whether a person's genetic make up could prevent them from benefiting from a medicine or whether they might be at risk in taking it.

QUALITY, SAFETY AND EFFICACY

While new techniques have made it possible to screen many more candidate medicines and have speeded up the initial discovery process, a potential treatment must be thoroughly tested before it can be authorised for general use. It will be constantly evaluated during its development in order to maximise its effectiveness and minimise any unwanted side effects. After initial testing using computer simulation, test-tube methods and animal testing, a promising compound begins three phases of clinical trials in an increasingly wide range of people, in order to analyse its effects in the human body and its absorption, distribution, metabolism and excretion.

The industry has issued proposals to set up a worldwide register of clinical trials, drawn up by the world's major industry trade associations and agreed by major companies. Results of all industry-sponsored clinical trials evaluating the benefit and safety of a medicinal product, regardless of outcome, will be disclosed via free, publicly accessible databases once it has been approved for use in patients. Details of all clinical trials being performed to determine a medicine's therapeutic benefit will be publicly registered at initiation, so that patients and clinicians will have information on how to enrol. The website to find out more about the register is **www.abpi.org.uk/press/press_releases_05/050701b.asp**

All new medicines have to demonstrate their quality, safety and efficacy to the medicines evaluation authorities – the UK Medicines and Healthcare products Regulation Agency (MHRA) or the European Medicines Agency (EMEA) – before they will be approved for use in the UK. All trials results, whether positive or negative, have to be submitted to

the authorities before approval. Clinical studies provide the authorities with reliable data about the efficacy and safety of new medicines, but they cannot reveal every rare side effect.

A medicine in clinical trials is generally tested in several thousand patients but, after authorisation, goes into use by possibly millions of people. Some side effects may occur in only one in 100,000 people. In order to reduce risks of side effects, some people have advocated limiting the initial use of new medicines to a restricted number of patients. This would make the identification of rarer side effects lengthier and more difficult, while at the same time restricting the benefits which the great majority of patients can gain from a new medicine.

After authorisation for use in the UK, the side effects of medicines are monitored through a variety of monitoring systems, including one known as Yellow Card reporting. Prescribers monitor their patients and may fill out a report card of individual adverse events, which is then sent to the MHRA, for assessment involving comparison with any others, both from the UK and other countries. Depending on the gravity of the side effect, the MHRA may add it to the medicine's Summary of Product Characteristics or in serious cases, issue an urgent safety report to prescribers or withdraw it.

The Yellow Card Scheme is particularly important and helps to ensure that information about such side effects is rapidly captured by the system and quickly passed on to other prescribers. The Yellow Card Scheme is underused in the UK and the industry supports moves to encourage increased monitoring by doctors of all patients' treatments, especially those involving new medicines.

Direct reporting by patients of adverse reactions was introduced in 2004, enabling patients to inform the MHRA of adverse events when taking a medicine. This is a move fully endorsed by the industry.

HOW MEDICINES ARE TESTED AND MONITORED

- 1. Initial research on new compounds is carried out in the laboratory *(pre-clinical development)*, using a wide variety of techniques.
- 2. Promising compounds are then studied in animals, subject to strict ethical and legal conditions, to investigate effects that currently cannot be predicted from computer and test tube studies.
- 3. A sequence of phases of clinical assessment in humans follows, under strict guidelines:
- **Phase 1:** a small number of people, either healthy volunteers or patients with the target disease, is given the compound. These trials are designed to establish dose limits for the compound and to measure some aspects of how it works in humans. They are generally not intended to determine efficacy.
- **Phase 2:** a larger number of patients with the condition are given the medicine to assess both that it works and that it does not produce unacceptable side effects. In some cases, Phase 1 and Phase 2 studies may be combined.
- **Phase 3:** many more patients, perhaps several thousand, take the medicine under appropriate supervision for an appropriate period. It is tested in comparison with an established compound and/or a placebo. These studies are used to establish the efficacy of the new medicine. If the results prove satisfactory in terms of quality, efficacy and safety, the data gathered are presented to the medicines evaluation authorities. If the evidence satisfies the authorities, i.e. the benefits versus the risks are acceptable, a marketing authorisation is issued.
- **Phase 4:** the newly-licensed medicine is studied in large numbers of patients in general practice to assess its clinical effectiveness and safety in general use.
- 4. **SAMM** (Safety Assessment of Marketed Medicines) studies are sometimes initiated after the medicine has been made available for doctors to prescribe and to help identify any unforeseen side-effects. These may involve many thousands of patients.
- 5. GP databases are also used to identify medicine safety issues and to explore the potential for new and better uses of medicines once the product is available for prescription.
- 6. Monitoring through the Yellow Card scheme helps to ensure that rare adverse side effects are picked up as early as possible. If a side effect is found to be serious, extra warnings may be issued or the medicine may be withdrawn. Patients can also report adverse reactions.

Stages in the discovery and development of a new medicine