Drug development: health and safety

Safety testing of drugs

Before being used in humans, drugs undergo rigorous safety testing

It typically takes more than a decade for a new drug to go from initial research to use in the clinic. During this time, companies have to show that their drug actually does something beneficial and that it is safe.

There are a host of regulatory processes that have been set up to ensure these criteria are met before a drug is made available. They are designed to protect the public from harmful drugs and modern-day snake-oil salesmen. But no drug is entirely without side-effects, and medicines can themselves be a source of ill health.

While companies developing conventional medicines must spend millions proving that their products work, there is less regulation of complementary and alternative medicine (CAM) products. In the EU, the Homeopathic Medicinal Products Directive and Herbal Medicine Directive aim to ensure the safety and quality of homeopathic and herbal medicines, but less than half of all European countries have any general laws on CAMs.

Snake-oil salesmen sold cure-all potions in the Wild West. The term is now used for anyone selling dubious medicines.

Use of animals in safety testing of drugs

The use of animals in safety testing is a key stage in drug development

In 1937, US company S. E. Massengill used diethylene glycol, a sweet-tasting chemical, to prepare a new formulation of the drug sulphanilamide, which was used to treat strep throat. But the sweet, syrup-like preparation had a sour aftertaste – more than 100 people, mostly children, died after taking it. Although Massengill's chemists studied the appearance, flavour and smell of their 'elixir of sulfanilamide', they did not test its toxicity; unfortunately, diethylene glycol is a poison.

In the 1950s, German pharmaceutical company Chemie Grünenthal GnbH began producing thalidomide (see 'Thalidomide and Vioxx'), which was used by pregnant women to help with morning sickness. It wasn't until 1961 that the drug was linked to disabilities in newborn babies – it's thought that more than 10,000 children were affected. The thalidomide case is sometimes used as an argument against animal testing – it was shown to be safe in animals – but in fact, the reverse is true. Despite being marketed as a remedy for morning sickness, it was never tested on pregnant animals to see whether it affected the fetus.

Both these cases led to a tightening up of drug-testing regulation. Animal testing determines whether the drug is non-toxic and whether it is absorbed by the blood, goes to the right part of the body, works effectively and is properly excreted. It can also reveal how it is metabolised – a single chemical may be converted into tens or even hundreds of metabolites in the body. Crucially, animal tests lessen the risk to human volunteers, the next stage in the drug development process.

So does animal testing perfectly predict what happens in people? No. Some drugs went through an animal screening stage yet still turned out to be toxic in humans. This is hardly surprising – rodents are similar to humans but obviously not identical. It is a question of reducing risk. The risk remains too high to leap from test-tube to human without the use of animal models.

Although there are alternatives that can substitute for some aspects of safety testing, nothing can yet model the complexity of a living organism. In the UK, medical researchers operate under the principles of the '3Rs': replacement, reduction and refinement and adhere to Home Office regulations. Replacement may involve using human volunteers or computer models instead of animals. The principle of reduction focuses on using only the number of animals necessary to collect the data required, and on maximising the amount of data that can be obtained from individual animals. Whilst refinement refers to improving standards of animal welfare in scientific research.

REFERENCES:

Sulfanilamide Disaster

https://www.nc3rs.org.uk/the-3rs

Thalidomide

http://broughttolife.sciencemuseum.org.uk/broughttolife/themes/controversies/thalidomide

The 3Rs

https://www.nc3rs.org.uk/the-3rs

The Northwick Park drug trial

A disastrous phase I trial in 2006 raised questions about the safety of drug testing

In March 2006, six healthy volunteers taking part in a phase I drug trial at Northwick Park Hospital, London, were given small doses of a new drug being developed for rheumatoid arthritis. The drug, a monoclonal antibody known as TGN1412, had been through animal testing, and the trial had been approved by the Medicines and Healthcare Products Regulatory Agency (MHRA).

Within an hour of receiving the drug, the first volunteer reported a headache and began to complain that he was 'burning up'. Within 24 hours all were in intensive care. Although none of the participants died, they all spent at least a month in hospital.

What went wrong? Intensive investigations revealed that the firm responsible for TGN1412 followed all appropriate safety regulations and the materials themselves were not contaminated.

The likely explanation is that the drug acted in unexpected ways in the volunteers, triggering a massive immune response. The drug had no such effect in the monkeys it had been tested on previously, even though they have a very similar version of the target molecule, a receptor on immune cells. Following the trials, other researchers questioned the suitability of the animal models used – very small differences in the protein sequence of the receptor may have been responsible for the dramatic difference in response in humans.

The *British Medical Journal* later questioned whether the authorities should have approved the trial. The drug targeted a key component of the immune system. Was it too risky to be trialled in people? Extra safeguards have now been put in place for agents that target the immune system in this way.

The case is a reminder that clinical trials are risky. Mercifully, extreme reactions like this are very rare. It also emphasises why phase I trials are so important. Safety is paramount, and lessons have been learned from the TGN1412 incident. Regulation has been simplified and streamlined in an attempt to collect as much information as possible about risk factors before a clinical trial is authorised.

It is hoped that in the future computers may be able to give us greater information about how a drug might react in the body. This, along with animal models, will hopefully prevent another case like Northwick Park from happening.

REFERENCES:

UK drug trial disaster – the official report

https://www.newscientist.com/article/dn9226-uk-drug-trial-disaster--the-official-report/#.U-nW_KVcJY5

TGN1412: From Discovery to Disaster

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2964774/

The calm after the cytokine storm: lessons from the TGN1412 trial

https://www.jci.org/articles/view/35382

Complementary and alternative medicines

Where do complementary and alternative medicines fit into modern medical practice?

Arnica for bruises, echinacea for colds: for millions of people the answer to the evils of modern life, from constipation to migraines, lies in complementary and alternative medicine (CAM).

The list of treatments is long and varied – Ayurvedic, Chinese and Tibetan herbs, acupuncture, chiropractic and reflexology. For some practices, there is scientific evidence of positive effects; for most, there is not.

Some people benefit from herbal medicines – many with long-term health conditions such as irritable bowel syndrome or chronic pain find them useful as a way of taking control of their health. Of course, the pharmaceutical industry has a long history of developing drugs from plant sources. However, herbal remedies are not prepared or tested in the same way as licensed drugs. So the issue is not that they definitely do not work (though many won't), but rather that we do not know whether they work or whether they are safe and cannot be sure what standards the formulations available are prepared to. Whilst a few herbal medicines have passed more stringent tests - there is now evidence that St John's wort is effective for mild depression, for example - it is difficult to recommend herbal medicines based on the information available. Cancer Research UK suggests using herbal medicines, including St John's wort and ginkgo, with caution, because they could interfere with the action of cancer drugs.

One popular but controversial CAM approach is homeopathy, founded 250 years ago by a German doctor, Samuel Hahnemann. He conceived the principle that 'like cures like'. For example, onions – which produce streaming, itchy eyes – might, in minute doses, relieve hay fever. But critics are scathing. Homeopaths dilute a substance so many times that the final remedy is unlikely to contain a single molecule of active substance. Although homeopaths propose that water may maintain a 'memory' of the active substance, there is no known mechanism by which homeopathy might work.

In addition, when put under scientific scrutiny, homeopathy fails to measure up. A recent analysis of well-conducted studies of homeopathy found no evidence that it was better than a dummy medicine (placebo). In the EU, the European Academies Science Advisory Council – representing 29 national academies including the UK's Royal Society – is calling for regulations to prevent the provision of homeopathic medicines via public health channels. It says the medicines are unsafe because they delay conventional medical treatment.

On the other hand, the placebo effect should not be rubbished. In a typical clinical trial, nearly a third of people given a placebo will respond positively (see 'The placebo effect'). The success rate of many drugs is not much better than that.

The source of dispute is whether CAM remedies work – and how this can be judged. With so many different therapies lumped under the same umbrella – some more dubious than others – it is impossible to give a straightforward answer. Support for CAM tends to be based on anecdotal evidence: a patient given a medication improves, therefore the medication works. But this is not accepted as valid evidence by the scientific community.

Conventional medicine uses randomised controlled trials as a stern test of effect. CAM practitioners respond that individualised treatment cannot be tested in this way.

Drug side effects

Despite the years of research and clinical trials, a drug may still turn out to have harmful side-effects

In 2016, a Turkish doctor reported that one of his patients, a 47-year-old woman with bipolar disorder, had told him that her normally straight hair was becoming curly. The only explanation, according to the doctor, was her medication – daily valproate, prescribed as a mood stabiliser. Writing in the journal *Clinical Psychopharmacology and Neuroscience*, he said, "She prefers curly hair and doesn't want to change to another mood stabiliser." It wasn't a complete one-off though. In fact, this rare side effect was discovered in the 1970s, when doctors at the Children's Hospital in Birmingham, UK, noted the effect in five of 250

patients they studied who were given valproate. One boy, they said, “was mortified by his curls and insisted on a short hair cut.”

Curly hair might be unwanted but it isn’t harmful. In another series of cases, patients using a particular group of drugs prescribed for Parkinson’s disease turned into compulsive gamblers. The effect was originally seen during routine visits to patients in the early 2000s – in one case a female patient lost US $100,000 and her gambling led to the break-up of her marriage. By 2015, it was clear that the effect was less rare than researchers originally thought and that between 7 and 32 per cent of patients – depending on the specific dopamine receptor-activating drug prescribed – were suffering from ‘impulse control disorders’. These included compulsive shopping and gambling disorders as well as ‘hypersexuality’, a preoccupation with sex.

Adverse drug reactions as a whole are surprisingly common. Roughly 6 per cent of all hospital admissions are due to adverse reactions to drugs, according to global figures from a 2016 study. In developing countries, reactions tended to be more severe. Some of the drugs most frequently causing hospitalisation included anti-blood-clotting agents, non-steroidal anti-inflammatories such as aspirin and ibuprofen, and heart medications. Researchers involved in the 2016 study say the majority of adverse reactions could be prevented by more careful use of drugs, particularly in patients taking a number of different medications.

Such statistics have to be set against the enormous benefits that pharmaceuticals bring, but they do illustrate that drugs are powerful agents. As well as seeking to discover new agents, pharmaceutical companies also work to reduce the unwanted side-effects of existing ones.

‘Safety’ is not an absolute: it involves a cost–benefit analysis, weighing up the risks with the benefits. These will depend on the drug, the nature of the illness, the availability of alternatives – and individual choice.

Thalidomide and Vioxx

This tale of two drugs serves as a reminder of what happens when serious side effects slip through the net

In the mid-1950s the drug thalidomide was used as an epilepsy treatment in Germany, despite a lack of supporting evidence. The drug had a sedative quality, and patients who received it reported a deep soothing sleep. By 1957, based on the drug’s ability to relieve nausea, it was being marketed as a treatment for morning sickness.

Although the effects on the mother were as expected, the drug proved fatal for many exposed to it in the womb. In 1961, a doctor working at an Australian hospital made a link between mothers who took thalidomide during pregnancy and disabilities in their children. The drug was taken off the market the same year in the UK and in the rest of the world by 1962. It had not been licensed in the US, due to misgivings about its safety at the Food and Drug Administration (FDA).

In all, it is thought over 10,000 babies were born with the effects of thalidomide and that many more were lost before birth. Less than about 3,000 survive today. After thalidomide, the regulation of drug testing was tightened considerably and systems introduced to report adverse reactions. Articles written by the FDA pharmacologist, Frances Kelsey, who blocked thalidomide’s approval in the US, laid the groundwork for modern drug testing.

Despite safety being much improved, the case of Vioxx illustrates that it is not infallible. Vioxx and related drugs were supposed to be good painkillers with fewer side-effects than existing drugs. It was launched in 1999, but almost immediately some researchers questioned whether it was really safe. In 2004, with global sales exceeding US$2.5bn (£1.2bn) a year, Merck withdrew the drug after a trial revealed a doubling of risk of heart attack and stroke.

In research published in *The Lancet*, it was estimated that Vioxx caused 88,000 heart attacks, leading to 38,000 deaths. Some critics accused the FDA, the USA’s drug-licensing body, of not doing enough to protect patients. In 2007, a settlement of nearly US$5bn (£2.5bn) was agreed for Vioxx lawsuits – meaning Merck did not get involved in any of the personal-injury lawsuits relating to 47,000 people affected by their drug.

REFERENCES:

Thalidomide

http://broughttolife.sciencemuseum.org.uk/broughttolife/themes/controversies/thalidomide

Thalidomide scandal: 60-year timeline

https://www.theguardian.com/society/2012/sep/01/thalidomide-scandal-timeline

About thalidomide

https://www.thalidomidetrust.org/about-us/about-thalidomide/

Thalidomide-induced teratogenesis: History and mechanisms

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4737249/

Lessons to learn from the COX-2 saga

https://www.health.harvard.edu/newsletter_article/lessons-to-learn-from-the-cox-2-saga

Timeline: The Rise and Fall of Vioxx

https://www.npr.org/2007/11/10/5470430/timeline-the-rise-and-fall-of-vioxx

Merck pulls Vioxx painkiller from market and stock plunges

https://www.nytimes.com/2004/09/30/business/merck-pulls-vioxx-painkiller-from-market-and-stock-plunges.html

Drugs and acceptable risk

What level of risk are we prepared to tolerate with medicines?

No matter how hard we try, no medicine will ever be perfectly safe. Many potential therapeutics are abandoned because they are deemed too toxic; some are introduced but are later withdrawn because of dangerous side-effects.

But have our expectations become too high? In the past, greater risks were accepted. Salvarsan, an early mass-produced drug containing arsenic, was used to cure syphilis but had nasty side-effects and was often itself fatal. Even today, another arsenic-containing drug, melarsoprol, is used to treat sleeping sickness in Africa. Up to 1 in 10 patients who take it suffer a severe immune reaction that leads to coma. About half of those patients who suffer the reaction die. Ironically, the alternative is risking coma and death as a result of sleeping sickness.

Over the past few decades, drugs have mostly become safer and with fewer side-effects. A major turning point was the thalidomide disaster (see ‘Thalidomide and Vioxx’), which highlighted important deficiencies in the way that new drugs were tested. We may have safer drugs now, but the numbers of new drugs being launched each year has dropped.

Developing drugs is now a long and expensive process. The pharmaceutical industry warns that excessive regulation – and the addition of new hurdles, such as cost-effectiveness – will reduce the number of drugs produced. Critics of the industry argue that companies use clinical trials creatively to get the results they want, or report data selectively, to secure licences and encourage use.

The Vioxx story has raised fears about the effectiveness of regulatory systems. There is ongoing concern about the side effects of other pharmaceuticals, such as certain antidepressants, which have been linked to increased suicide risk. Unlike with thalidomide, the link between medication and an adverse effect may not be not clear-cut, and may often be disputed. The risks may also be manageable if identified.

But there is another side to the Vioxx story. It still has its uses, and some people might be willing to accept a known risk. The manufacturer Tremeau Pharmaceuticals has plans to bring it back to market for people

with haemophilia who are not able to use non-steroidal anti-inflammatory drugs like aspirin and ibuprofen. It's a difficult balancing act. Not only do we want safe drugs, we also want the best treatments possible. Over-regulating drug development will ensure that drugs are safe but may hinder pharmaceutical companies in supplying the best treatments that current technology can provide. Likewise, under-regulating will allow more drugs to make it to market but could allow dangerous mistakes to happen.

Post-approval safety monitoring of drugs

Monitoring of a drug's safety continues even after it is prescribed to patients

Clinical trials can ensure a new drug is safe to use (or that its benefits outweigh its side-effects – no drug is completely safe). But even the biggest trials only include a few thousand patients for a limited period of time. When a drug is finally used in 'real life', rare side-effects may appear.

To capture these effects, most countries run a monitoring or pharmacovigilance system.

In the UK, the Medical and Healthcare products Regulatory Agency (MHRA) is responsible for monitoring new drug safety. This relies mainly on spontaneous reporting from doctors and other healthcare professionals via the yellow card system, named after the coloured slips that doctors complete to record side-effects. This system was introduced after the thalidomide episode. Although it's useful, it has drawbacks – it's likely to under-report adverse reactions, and it's up to doctors to decide whether a reaction is linked to drug use.

In 2005, the yellow card system was expanded to patients so that they could also report incidents via the internet.

In the 1980s, a complementary system – prescription event monitoring – was set up. This captures details of any adverse effect, usually in the first 10,000 people given a drug, tracked through the prescription system.

In Europe, pharmacovigilance is currently coordinated by the European Medicines Agency, which draws information from national bodies and maintains a database of adverse drug reactions. This system can provide a warning about drugs that seem to be causing harmful reactions.

REFERENCES:

Yellow card scheme

https://yellowcard.mhra.gov.uk/

Modified prescription-event monitoring studies: a tool for pharmacovigilance and risk management

https://www.ncbi.nlm.nih.gov/pubmed/22077508

Drug-resistance in disease

Drug-resistant bacteria can mean that some treatments become ineffective over time

Aspirin works as well today as it did when launched. But drugs used to treat infections (and cancer) lose their potency, because of resistance.

The headlines send a chill down the spine. 'Killer bugs' or 'superbugs' have found a way around the drugs we use to destroy them. From MRSA (methicillin-resistant *Staphylococcus aureus*) to tuberculosis, resistant bacteria are on the rise. And the threat is not confined to bacteria. The malaria parasite, the human immunodeficiency virus (HIV) and even tumours can develop resistance to chemotherapeutic agents. What's going wrong? Why are life-saving drugs losing their punch?

The answer is natural selection. Whenever microorganisms are placed under selective pressure, such as exposure to drugs, occasional mutant forms that are less susceptible to the drug survive. Whilst drug-

susceptible forms are still thwarted by the drug, the drug-resistant forms continue to multiply and can be transferred to other people.

There are many ways in which resistance to a drug may arise:

- Pump it up (and out): A microbe may expel a drug before it has a chance to act, using protein pumps in their cell membranes. Interestingly, cancer cells use a relative of bacterial pumps, the P-glycoprotein, to expel anticancer drugs.
- Chop it up: A common response is to metabolise a drug, breaking it down or chemically modifying it, rendering it ineffective. For example, some bacteria responsible for hospital-acquired infections produce enzymes to break down antibiotics.
- All change: A drug will act on a specific part of a target protein; if a mutation alters that part of the protein, the drug may bind less well and be less effective. The mutant protein may not work as well either, but at least the cell survives. Other mutations may then act to improve the protein's function.

In fact, resistance is rarely all or nothing. A bacterium typically first tolerates a drug – it survives but does not grow – before gradually becoming more resistant.

Resisting resistance

The development of resistance is simply natural selection in action, so it can never be completely avoided. But there are ways to minimise its impact.

One is simply to develop new medicines. This is more easily said than done, however. Developing a drug is expensive and takes years.

Another solution is to use drugs in combinations. If a microorganism acquires a mutation that makes it resistant to one drug, it will still be killed by another. It is extremely unlikely that the same cell will simultaneously acquire mutations protecting against all drugs being given together. Combination therapy is now used for tuberculosis, HIV/AIDS, cancer and some malaria treatments.

Another possibility is to rotate drugs, to allow them to lie 'fallow'. Over time, use of drug X in a region could lead to the appearance of resistance. That region could swap to drug Y, then later to drug Z. By the time resistance to drug Z appeared, the microbe might be susceptible to drug X again. There is some evidence from Africa that resistance to some antimalarials drops away once a drug is no longer used.

Another option is to reduce the spread of resistance in the first place by ensuring that all drugs – including anti-infective agents – are only used when they are necessary. This means, where possible, avoiding giving out antibiotics when it is not clear that they would be effective, for example, when a patient is suffering a viral infection that cannot be treated with antibiotics. Of course, it does not mean withdrawing the option of antibiotics from patients with high-risk infections that are unconfirmed.

For a long time, health authorities have recommended ensuring that antibiotics are taken at the dose prescribed until the course is complete; the rationale being that low doses may allow moderately resistant bacteria to survive and spread. Recently, this notion has been challenged on the basis of limited evidence, but, at least until further notice, the National Health Service (NHS) in the UK recommends sticking to current guidelines.

REFERENCES:

How antibiotic resistance happens

https://www.cdc.gov/drugresistance/about/how-resistance-happens.html

Drug-resistant infections: transforming the global response

https://wellcome.ac.uk/what-we-do/our-work/drug-resistant-infections

Balancing risks and benefits in the critically ill

Does a terminally ill patient have the right to take potentially life-saving drugs that may not be safe?

No one wants to see someone die of a terrible disease, especially if a drug exists that could potentially save them. But what if the drug is unproven? Controversy erupted in 2013 after Josh Harvey, a seven-year-old American boy, was refused unlicensed drugs that could potentially cure a crippling viral infection. Josh had become infected while on immunosuppressant drugs after a bone marrow transplant to treat his cancer. The drugs weaken the immune system to prevent transplant rejection, making the patient extremely susceptible to any kind of infection.

A social media storm put the small biotechnology company Chimerix under immense pressure to supply Josh with the drugs. After initially refusing, claiming that it was too costly, Chimerix bowed to the pressure in March 2014. Josh was in hospital for several months but eventually left for home in July 2014.

Despite the success of this story, drug testing is in place to ensure that drugs are safe and effective for critically ill people. Some argue that once those rules are bent, the whole system is undermined, which would open the door to unscrupulous people selling bogus potential cures to vulnerable people.

Nevertheless, setting society's needs against the incredible pain of a family with a dying child must be one of medicine's toughest ethical dilemmas.

A gamble with nothing to lose?

Drugs that haven't undergone substantial safety testing pose a much higher risk to the health of the patient. Still, critically ill people, or their families, may decide they want to gamble on an unproven drug. In 2003, the father of a 19-year-old victim of vCJD – the human form of mad cow disease – took an NHS trust to court to secure an untested treatment for his son.

After a long battle, the courts allowed the blood-thinning drug pentosan polysulfate to be infused into the teenager's brain. Jonathan Simms became one of the world's longest survivors of vCJD, but eventually died of the disease in 2011. A 2014 study found no evidence that the drug halted the loss of brain tissue in vCJD, but could not rule out the possibility that the pentosan polysulfate helped people live longer. With small numbers and no control group, it is difficult to draw any firm conclusions.

More recently, in 2017, a Texas man called Joe Tippens, who had been diagnosed with stage 4 lung cancer that had spread to his stomach, bladder and bones, was advised by a vet to start taking dog de-worming tablets. The tablets contained fenbendazole, a compound that was in the earliest stages of investigation as a cancer-killing agent. Joe later told national newspapers that taking the tablets cured him of cancer and that he was discharged by his oncologist in 2018.

Joe's story was partially supported by a 2018 paper in the journal *Scientific Reports* showing that fenbendazole causes cancer cell death in the test tube. The drug had not been through clinical trials in humans, but by 2019 Korean news sites were reporting that Korean cancer patients were 'rushing' to buy the dog pills, leaving veterinarians out of stock. Meanwhile, the Korean Ministry of Food and Drug Safety was warning patients against using it because it was unsafe, especially for patients weakened by chemotherapy.

While sympathy must be with critically ill patients anxious to try anything that might help, the case again raises difficult questions. Fenbendazole could well have harmful effects in people. Because the patients are not in a clinical trial, no useful data that might help others are being gathered. And if people die while taking fenbendazole, it might harm the chances of proper clinical trials being organised in the future.

Untested drugs are extremely risky. They could trigger unpleasant side-effects or even hasten death. The fact is that eight out of ten drugs that enter clinical testing are dropped because they are too toxic or simply don't work. In recent years, expanded access regulations have made it easier for critically ill people to be treated using drugs that are still in development, but this remains a highly contentious issue.