A Guide to Cancer Drug Development and Regulation

This booklet has been produced and will be distributed as a service to the oncology community by AstraZeneca
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Disclaimer
The information in this booklet is not intended to be a substitute for medical advice and you should contact your doctor in the event of you having concerns related to any of the matters discussed in this booklet.
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The concept of protecting the public from unscrupulous medicines stretches back to the 19th century. However, it was not until 1938 that the Food Drug and Cosmetic Act in the USA brought cosmetics and medical devices under control, required that drugs be labelled with adequate directions for use and stated that manufacturers would have to prove to the Federal Food and Drug Administration (FDA) that a drug was safe and especially, that it was not making any false claims, before it could be sold. A major change in drug regulation occurred in the late 1950s and early 1960s, when thalidomide, a drug given to pregnant women to stop morning sickness, was found to produce severe birth defects. The children of women taking the drug were born with abnormally small, sometimes virtually non-existent, arms and legs. This tragedy forced the pharmaceutical industry, the medical establishment and society in general to focus on drug safety. So legislation was introduced to protect the public from potentially dangerous drugs, and drugs cannot now be prescribed or sold without a licence or marketing authorisation.

No drug or medical treatment is entirely without side effects; the usefulness of any medication rests on the benefits it brings outweighing the side effects. Sometimes, both efficacy and side effects are highly dose dependent, for example low-dose aspirin can reduce heart disease, but constant consumption of higher doses can produce fatal stomach bleeds. Other simple “household” drugs such as paracetamol, while useful at the correct dosage, can be fatal if abused and taken in “overdose” quantities. For most medicines the skill in developing the correct dosage is finding the level at which maximal therapeutic benefit occurs with minimal side effects. For some drugs this is easy – for others it is more complex.

When a drug is approved, or licensed for prescribing, it effectively means that regulatory bodies have satisfied themselves that the drug in question produces benefits that outweigh the disadvantages. However, even when drugs have been tested extensively and granted marketing approval we must not be complacent that we know everything about their side effects. Recent scares surrounding some cox-2 inhibitors, widely used to treat certain types of chronic pain, whose serious side effects compromised the value of the drugs and precipitated withdrawal of some drugs in this class, are a reminder that even when medicines are thought to be “safe” they can sometimes have untoward side effects that only become apparent when they are given to a very large number of people.

So the considerations surrounding drug licensing are complex. There are no absolutes and the licensing of useful drugs requires considerations of risk–benefit balance – considerations that will be influenced by the nature and severity of the condition being treated. A medicine aimed at a life-threatening cancer might be acceptable even if it displays potentially unpleasant or serious side effects – one to treat headache would not!

It can take many years, and an enormous investment, to develop a medicinal product and have it approved for a specific disease and circumstances. The science and legislation underpinning drug development and regulation are constantly evolving. The terminology used is highly technical and can be difficult to understand. It is not surprising, therefore, that many different aspects of drug development and regulation are not widely understood. Most cancer patient representatives are poorly acquainted with the intricacies of drug regulation, yet increasingly patients are being called upon, or seeking to have, a voice in these processes. In order to be able to play a more active role in the development and regulation of cancer drugs, patient advocates need a better understanding of the scientific, legal and regulatory aspects of drug approval. It has been estimated that
nearly 400 cancer products are currently in clinical development or undergoing regulatory review, and patient involvement with licensing may be sought for a number of these drugs. The purpose of this booklet is to help the reader understand how cancer drugs are developed and regulated.

Drugs have two names: the generic name (also called the International Non-proprietary Name or INN), which is the name of the active substance, and the proprietary or brand name. Currently, if a drug is marketed by more than one company, it may have more than one proprietary or brand name. (For example, you probably own a vacuum cleaner, which may be a Hoover brand, a Dyson brand or some other make; but they are all vacuum cleaners). Brand names may also vary throughout the world, whereas generic names do not (except in different languages). However, there is a move towards unification of brand names so that they do not vary internationally.

This booklet is concerned with the approval of prescription-only medicines (POM) – drugs which can only be prescribed by a qualified medical practitioner. It does not cover the regulation of other classes of drugs: pharmacy-only medicines (P), which can only be bought from a pharmacist, and over-the-counter (OTC) medicines, such as aspirin, which can be purchased freely in a shop or supermarket. Where specific drugs are mentioned, the generic names of drugs are used with the brand name in brackets.

Using this booklet

There are numerous complex terms used in this booklet, which are explained in the text and also in the glossary. The first time a new term is used it is printed in coloured text; this colour denotes in which chapter the word first appears. The same colour coding is used in the glossary, so if you look up a word you can identify in which chapter it was first used. It is hoped that all terms have been clearly explained, but if you start reading in the middle of a section, it may be that the explanation has been given earlier in the section.

The processes involved in drug approval are explained in outline only, using the US and European systems as examples; this is not to ignore other countries, but it is impossible to cover them all. More details on the US and European systems are given in the appendices, and websites are listed that provide full details of country-specific information. The websites handle the information in very different ways and some websites are easier to navigate than others! The FDA is the only agency with a special section on cancer drugs on its website.
Chapter 1:
Overview of Cancer Drugs
As often happens in science, the discovery of the first anti-cancer agent, nitrogen mustard, was an accident. Soldiers exposed to mustard gas during the First World War showed marked reduction in lymphoid tissue (tissue that produces a type of white blood cell called a lymphocyte, as well as antibodies). This observation led to the development of a derivative of mustard as an anti-lymphoma drug, and thus, in the 1940s, the modern era of chemotherapy was born. Since then our understanding of the biology of tumours and our ability to design effective drugs has reached a degree of sophistication unimaginable in those early days, and the current list of cancer drugs now runs to over 60 agents of varying types.

What is cancer?

Cancer is not one disease but many – it is estimated that there are over 200 different types of cancer. Cancers vary according to the part of the body where they first occur. There are also several types: carcinomas are cancers that begin in the skin or in tissues that line or cover internal organs (e.g. stomach, bowel, ovaries, prostate glands etc.). Sarcomas are cancers that begin in bone, cartilage, fat, muscle, blood vessels, or other connective or supportive tissue. Leukaemias are cancers that start in blood-forming tissue such as the bone marrow; they cause large numbers of abnormal blood cells to be produced and enter the bloodstream. Lymphomas and multiple myeloma are cancers that begin in the cells of the immune system. Cancers are characterised by their ability to grow, invade local tissue and metastasise (i.e. spread through the bloodstream and lymphatic system to other parts of the body where they form metastases or “secondaries”).

Cancer can occur at any age, but it is much more common in people over 65 years old. As the world’s population ages, it is likely that we will see a large increase in the incidence of cancer over the next 20 years.

The commonest cancers occur in the lung, bowel, prostate and breast – less common cancers occur in the different body systems including the blood and lymphatic system and the brain. When doctors diagnose a cancer they categorise it according to its stage. Staging is based on the size of the tumour, whether lymph nodes contain cancer, and whether the cancer has spread to other parts of the body. So a stage 1 or early cancer will be small, discrete and locally confined; a stage 2 cancer may be larger and may have started to spread to the lymph nodes, stage 3 has spread to lymph nodes, probably more than one, whereas a stage 4 or advanced cancer will be larger, more diffuse and will have spread not only to lymph nodes but to other parts of the body.

The details of the staging system vary according to cancer type; however, all provide an indication of how extensive the disease is (i.e. early or advanced). The earlier a cancer is detected, the more likely it is to be curable.

How do cancers develop?

The majority of cells in the body are capable of growing and dividing into two new cells. This process is necessary to replace worn out and damaged cells. Cell growth is very carefully regulated and highly ordered, with a number of delicately balanced controls in place to make sure that cells are only produced as and when they are required. When stimulated appropriately, by the correct signals, cells enter the cell cycle where they go through four different phases in order to divide and produce two new cells. Otherwise, cells just sit at rest until a new signal is received. In this way, cells grow in the right place, at the right time, and the correct numbers of cells are produced.
Cancer is unregulated and disordered cell growth. Tumour cells ignore the factors that control normal cell growth and develop into a mass or tumour that is capable of growing into surrounding tissues and metastasising to other parts of the body. It can take many years for a tumour to grow and develop into a mass that is visible by modern imaging techniques (e.g. CT scan, MRI, mammography etc.).

**What drugs are used to treat cancer?**

Cancer drugs can be grouped into four broad classes:
- Cytotoxic drugs
- Endocrine (hormonal) therapy
- Targeted therapies – this includes small molecules and antibodies
- Vaccines

In addition, there are supportive therapies, which are employed alongside the cancer drugs to reduce the impact, and consequences of treatment, or side effects, or to relieve symptoms in people who are no longer treatable (palliative care).

Examples of these types of drugs include:
- Erythropoietin stimulating proteins (ESPs), which help the body restore a normal level of red blood cells after chemotherapy, so alleviating the anaemia and fatigue associated with treatment
- Granulocyte colony stimulating factor (G-CSF), which is used to reduce the neutropenia (lack of white blood cells) caused by cytotoxic drugs. Neutropenic patients are more susceptible to infection
- Bisphosphonates, which are used to treat bone metastases and hypercalcaemia of malignancy (high calcium levels in the blood)
- Anti-emetics, used to alleviate the nausea and vomiting produced by chemotherapy
- Analgesics, used to alleviate cancer-related pain
- Keratinocyte growth factor, used to prevent mucositis (soreness and ulceration of the mouth) associated with chemotherapy.
How are drugs used to treat cancer?

There are basically three ways of treating cancers: surgery, radiotherapy and drug therapy, which are used alone or in combination. Surgery and radiotherapy are local therapies used to eliminate discrete tumours. Drugs, by contrast, act systemically (throughout the body). So cancer drugs reach practically every part of the body, and can be employed not only to attack the tumour, but also to reduce the chances of metastases by killing individual cancer cells that may have detached from the main tumour – even when the spread is still too small to be detected by radiological or laboratory tests.

Cancer drugs are used in a variety of ways. They can be given before surgery to reduce the tumour size and make it easier to remove (called neo-adjuvant therapy). They may be the main form of treatment, or are given following surgery and radiotherapy in order to reduce the chance of a tumour recurring (called adjuvant treatment). Drugs may also be used with the intention of reducing the tumour size and alleviating symptoms in patients with advanced cancer, even though the cancer may be inoperable.

Normally a drug treatment plan that specifies the dosage, the schedule, and the duration of treatment is developed. These treatment plans are called regimens. The initial regimen prescribed for a patient is determined by many factors including the tumour type, characteristics and stage, the availability of evidence-based guidelines that support the regimen’s use in this situation, physician experience and patient choice. These regimens may differ slightly from clinic to clinic or between countries; some may be widely accepted as standard, but there is no one single treatment that is universally accepted for any given tumour type.

The effect of a particular treatment regimen may vary from patient to patient. A surgeon may be able to remove a discrete tumour completely, but in other cases only partial resection may be possible. A patient may not respond to radiotherapy because their tumour is radio-resistant. Sometimes, a tumour does not respond to the first chemotherapy treatment used, or an initial positive response may not be maintained, because the tumour has become resistant to the treatment (chemotherapy resistant). If this happens patients usually have the option of having further treatment with a different drug regimen (also called salvage therapy). Some cancer patients may have as many as 10–15
different salvage treatments (also called lines of treatment; i.e. 1st line, 2nd line, 3rd line and so on) that are given sequentially over a period of time. Tumours that do not respond to chemotherapy treatment are said to be refractory.

Cytotoxic drugs

An early approach to treating cancer was to use drugs that kill growing and dividing cells (i.e. those going through the cell cycle). Drugs that kill dividing cells are known as cytotoxic drugs (cyto = cell and toxic = killing or poisonous). The use of cytotoxic drugs to kill cancer cells is really an indiscriminate approach since, unfortunately, these agents kill not only tumour cells but also other normal dividing cells in the body. This gives rise to the well-known side effects of increased risk of infection, fatigue, hair loss, and severe nausea and vomiting, as the cells of the immune system, the blood, the hair follicles and the gut are also affected by the drugs.

We now understand the cell cycle in great detail, and can classify cancer drugs into different groups depending on where they act in the four phases of the cycle. Cytotoxic drugs are normally given in combination, using drugs that:

• are effective against the tumour
• act at different points in the cell cycle
• have different side-effect profiles

In this way the dividing cancer cells are attacked at every point of their cycle without increasing the severity of side effects. Cells can also become resistant to the action of drugs. Combining several drugs can help overcome different mechanisms of resistance.

A treatment plan with cytotoxic drugs normally involves giving the drugs in cycles: a treatment period followed by a recovery time to allow normal cells to recover, then another treatment period. A course of treatment will consist of a defined number or cycles of treatment, given over a period of weeks or months. Treatment courses vary according to the tumour type and stage (i.e. whether the cancer is early or advanced).

The dose of cytotoxic drug given is tailored to the individual patient. Normally the physician will work out the patient’s body surface area, or measure their weight, and calculate the dose of drug to prescribe based on these parameters.

Hormone therapy

Hormones occur naturally in the body and they control the growth and activity of normal cells. Some tumours have been found to grow under the influence of hormones. For example certain breast cancers are stimulated by oestrogen, a normal female hormone, and cancer of the prostate initially depends on the male hormone testosterone for its growth. Hormonal therapy, also known as endocrine therapy, acts to block a patient’s natural hormone activity or reduce the hormone levels and so starve the tumour of an important substance that is encouraging growth. Hormonal therapy can be used in the early or advanced cancer setting. In the adjuvant setting the drugs are normally taken for several years and are given as daily tablets or monthly injections.
Targeted therapies

The tremendous advances in scientific knowledge that have occurred over the past two decades now allow us to focus drug activity far more precisely onto tumour cells. The idea behind targeted therapies is that there are differences between cancer cells and normal cells in terms of their genes or the proteins in the cells. Targeted therapies exploit these differences by targeting the very factors that are different in the cancer cell. So by blocking the molecular pathways that transmit the pathological signals that are driving the cancer process, the therapy attacks the cancer cell without disrupting the functions of normal cells and tissues.

Targeted drugs work in a variety of different ways. Small-molecule drugs are usually able to get inside the cell to block specific pathways, preventing the cells proliferating and causing cell dysfunction and death. They inhibit certain enzymes in cancer cells and they can be recognised because they contain a “nib” (from inhibit) at the end of their name (e.g. imatinib, erlotinib, sorafenib, sunitinib, dasatinib etc.). These small-molecule drugs are normally taken by mouth. There is a growing number of this type of drug.

Large proteins, such as monoclonal antibodies, attach themselves to receptors on the surface of the cancer cells and stop signals being sent into the cell.

Figure 2: Targeted therapies
Monoclonal antibodies are normally given by injection, since they would be destroyed by stomach juices if taken orally. They can be recognised because of the “mab” at the end of their name (e.g. trastuzumab, rituximab, cetuximab etc.).

A major difference between small molecules and large proteins is the length of their half-lives. The half-life of a drug is the time it takes to be eliminated from the body. So drugs which are proteins have very long half-lives and will stay in the body for a long time (e.g. if the half life is 60 days, half the original quantity of drug is still in the body at 60 days, failing to half that quantity 60 days later and so on until all the drug has disappeared). Small molecules, by contrast, have very short half-lives, often measured in hours, so that all the drug will be eliminated quite quickly. This is an important consideration for people who react to the drug or who may need to be “drug free” for surgery.

Targeted therapies in development include agents that prevent cell growth or proliferation as well as drugs that inhibit the invasive nature of tumour cells and thereby inhibit the formation of metastases. Some targeted therapies cause apoptosis of cancer cells (i.e. spontaneous cell death), and others are angiogenesis inhibitors, which block the growth of new blood vessels, thus interfering with growth and metastasis of solid tumours.

The first targeted therapies to be developed were directed at a single signalling pathway that was involved in tumour growth, but as our experience with these agents grows, therapies directed towards multiple targets are being developed. This means that the targeted therapies may be attacking the tumour cell dysfunction at more than one point. Sunitinib (Sutent) and sorafenib (Nexavar) are examples of multitargeted therapies. (These particular agents are called multikinase inhibitors, because they are targeted at more than one of the cell’s kinases - important enzymes in cells that are often altered in cancer).

A number of targeted therapies are available today for use against different cancers. Examples include those that target:

• Vascular endothelial growth factor receptor (VEGFR) – VEGFR is involved in the formation of new blood vessels (angiogenesis), which are needed to deliver oxygen to the tumour cells. Agents that block VEGFR, such as bevacizumab (Avastin), are known as angiogenesis inhibitors.

• Epidermal growth factor receptor (EGFR) – Overexpression of EGFR (also known as HER 1 or ErbB1) stimulates tumour growth. Drugs that block EGFR, e.g. cetuximab (Erbitux) for metastatic colorectal cancer, block the signal from growth factors which stops excessive tumour growth, and also increases apoptosis.

• HER 2, also known as HER2/neu or ErbB2, is overexpressed in certain cancers, stimulating tumour growth. It can be blocked by drugs such as trastuzumab (Herceptin).

• Abl tyrosine kinases – these include bcr-abl and c-kit, as well as the platelet-derived growth factor (PDGFR) tyrosine kinases; they have a number of effects on tumour cell growth. Imatinib (Glivec) is an example of a bcr-abl tyrosine kinase inhibitor.

• Proteasomes – these are enzyme complexes that help regulate cell function and growth. Drugs such as bortezomib (Velcade) which inhibit the action of proteasomes, cause cancer cells to die by affecting multiple signalling pathways in tumour cells.

Molecular targeted therapies are often cytostatic that is, they stop cells growing or proliferating, rather than actually killing them (cyto = cell; static = still or stop). Because these therapies are targeted at cancer cells they are less harmful to normal cells and tissues and therefore cause fewer side effects than cytotoxic drugs. Common side effects include hypersensitivity reactions, high blood pressure, rashes and other skin changes and diarrhoea. The extent and type of side effects that they produce varies across drugs. They are rarely life threatening; however, they present a number of challenges for patients, who may need to stay on treatment for a long time, possibly the rest of their life.
Cancer drugs of the future

Gene therapy
There are several types of gene therapy. In some forms the faulty gene responsible for the cancer can be identified and a perfect version of this gene introduced into cells to override and compensate for the faulty one. Sometimes genes are introduced into the cancer cells to make them more sensitive to cancer therapy, or more sensitive to the body’s own immune system that will then destroy them. Some genes are introduced into the cancer cells and then activated to produce a toxin lethal to that cell type. No gene therapy is currently licensed for use in the treatment of cancer.

Vaccines
Cancer vaccines are being developed to treat cancer (therapeutic vaccines). These vaccines are designed to strengthen the body’s own immune system and stimulate it into attacking the cancer cells. These types of vaccines may prevent the further growth of existing cancers, prevent recurrence of treated cancers or eliminate cancer cells that have already developed. Vaccines are being investigated in breast, colorectal, lung and renal cancers and in B-cell non-Hodgkin’s lymphoma, but none are currently licensed.

Genes can be introduced into cancer cells to make them more sensitive to chemotherapy or more easily attacked by the body’s own immune system.
In contrast to treatment vaccines, there are also vaccines that guard against cancer developing, in the same way as we currently use vaccines against common diseases such as measles or polio (prophylactic vaccines). These are really vaccines against the cancer-causing viruses such as hepatitis B. (A few, but certainly not all, cancers can be shown to be caused by viruses.) Hepatitis B infection causes over 80% of liver cancers and early immunisation against this virus is advocated in order to reduce deaths from liver cancer.

Vaccines against human papilloma virus (HPV), responsible for cancer of the cervix (neck of the womb), have been developed and the FDA and the EMEA have just licensed quadrivalent human papilloma virus (types 6,11,16,18) recombinant vaccine (Gardasil), a vaccine that protects women against 70% of cervical cancers.
How are cancer drugs developed?

There are nearly 400 new cancer products in development today. Many of these potential new medicines will fail during development, but some may become important new treatments of tomorrow. The process of drug discovery is complex, time-consuming, uncertain and very expensive. It can take between 10 and 15 years to develop a drug, at a cost of about US$800 million. For every 5000 compounds tested, it is estimated that only one will be approved for use in patients. In this section we will detail the multi-step process of drug development – from the laboratory bench to the patient.

Drug discovery

The first step in making a new medicine is to define a specific target or parameter that plays a role in the development of a particular cancer. Cell lines are then chosen or developed that show properties similar to the cancer under consideration. Scientists then screen thousands of compounds – or chemically engineer new ones – to identify compounds that show some activity on these cell lines grown in the laboratory. Once identified, these molecules may need to be modified to increase their activity or minimize side effects. Hundreds of potentially active compounds are identified through this process.

Preclinical testing

Cells growing in a dish are not the same as cells in a body, so the compound must now be tested in animals, mostly mice and rats, to evaluate its safety and demonstrate that it has biological activity against the disease target. Regulators insist that agents are tested in animals first, to make sure that they are reasonably safe for the first dose to be given to a human.

Testing can take from three to six years and involves taking the compound though a variety of
toxicological tests (to show that the drug is not toxic and is safe), and teratogenicity tests (to show that they do not produce birth defects when given to pregnant animals). These tests are usually carried out in at least two different species, for example, the mouse and the rat.

The agents will also be tested against tumours in laboratory animals. They will then be tried against human tumours which have been grown in mice to test that the agents are active against human as well as murine (mouse) tumours.

In order for a compound to be selected to move on to further testing scientists must consider:

• Is the compound likely to be more effective than current therapies?
• Will the compound have a better safety profile?
• Will it be possible to manufacture and formulate the compound on a large scale?
• Does it have a reasonable dose range and delivery mechanism?

A compound may fail at this stage for a number of reasons – sometimes because it is not possible to manufacture it safely or consistently. Once a promising compound has been identified in the laboratory, it begins years of preclinical and clinical testing.

A huge amount of data must be collected on how the drug behaves in animals because, as well as showing that it has anti-tumour activity, scientists must also understand how the drug is absorbed and how it is distributed in the blood and tissues, metabolised (broken down by the body – most often in the liver) and excreted from the body; these are called pharmacokinetic studies. The way the body handles the drug – the relationship between drug concentration and effect – must also be investigated. These are called pharmacodynamic studies.

Most importantly, there must be no sign that the side effects of the drug are unacceptable or dangerous. Many drugs are dropped at this stage and do not undergo further development, because they fail one or more of these tests. It has been estimated that only 1 in 1,000 agents pass these tests successfully.

In addition to biological tests, scientists will examine the compound’s purity, stability and shelf life and evaluate what will be involved in producing this potential medicine on a large scale.
Formulation

The next stage in drug development is to produce an acceptable formulation of the drug. Drugs can be given orally (pill or tablet), or can be injected under the skin (subcutaneous), into the muscle (intramuscular) or into a vein (intravenous). The choice is determined by the chemical properties of the drug. If a drug can be given orally – as is usually the case for small molecules such as imatinib (Glivec) – it will be, as this is the simplest route of administration. But many drugs cannot be given this way, either because they are destroyed by digestive enzymes in the gut, because they do not get absorbed properly, or because they are potentially damaging to the gut. Large proteins such as monoclonal antibodies (e.g. trastuzumab, cetuximab) are examples of drugs that must be given by injection because they would be destroyed in the gut.

If drugs can be absorbed satisfactorily from a subcutaneous (under the skin) or intramuscular (into the muscle) site, then this route may be used, as these are the simplest type of injections to administer. This is useful for drugs that patients self-administer (for example, insulin or haematopoetic growth factors such as ESPs or G-CSF). But for medicines that cannot be absorbed smoothly from these sites or that have the potential to damage the skin and muscle tissue, the intravenous route is preferable. Intravenous administration ensures that all the drug is delivered into the blood system, and as it is diluted by the blood, the potential to harm tissue is minimised.

Some medicines are inhaled if they can be successfully absorbed from the lungs, and this route is also favoured for its simplicity. Scientists are trying to produce inhalational versions of drugs that are currently injected, such as insulin, but there are no cancer drugs that are given by inhalation.

Drugs normally take the form of a very small amount of powder or liquid; other substances called excipients need to be added so that it can be made suitable for administration. Excipients must be inert, i.e. they must have no pharmacological activity and the body must not react to them. Also, they must not affect the drug’s activity. Substances may also be added to ensure the drug’s shelf-life and sterility.

Clinical trials

While early preclinical research is essential in drug development, it cannot predict exactly how a new drug will work in humans and what side effects will occur. So, compounds that show promising preclinical activity must be tested in humans in a clinical trial. Of every 50 compounds that enter preclinical testing, only one will make it to the clinical trials stage. Clinical trials allow us to test whether a new drug is first safe and then effective in people with the disease and whether it has advantages over currently available therapies (for example, it may be more effective, may have less serious side effects or may be easier to administer).

What types of clinical trials are carried out?

There are four clinical trial phases. Each one is designed to answer specific questions about a drug’s safety and effectiveness.

Phase I trials are the first step in testing a new agent in humans. These studies evaluate the agent’s safety profile, what dose is safe, how it should be given (the appropriate formulation) and how often. Small groups of healthy volunteers or patients, called cohorts, are treated with increasing doses of the new therapy to find the highest dose with an acceptable level of side effects. This is the dose that will be used in future studies (called the maximum tolerated dose for cytotoxic drugs or optimal biological dose for targeted or biological therapies).

Phase I clinical trials of non-cancer drugs are usually carried out in healthy volunteers. However, because even useful cytotoxic drugs may have carcinogenic or teratogenic potential, phase I trials in cancer are
normally carried out in patients who have failed other therapies, and therefore have no further treatment options. Because of the better safety profile associated with targeted therapies, it is becoming more common to see very early trials of these agents carried out in human volunteers. Phase I studies take six months to one year to complete. Participants in phase I trials do not need to have measurable disease – inclusion of patients with evaluable disease is acceptable (measurable disease denotes a tumour that can be visualised by some imaging technique and measured objectively, evaluable disease is one where the presence of a tumour can be detected, but for technical reasons the tumour size cannot be measured).

Phase II trials have the goal of establishing the “proof of concept” – that the medicine could be potentially effective in treating patients with a particular disease. Phase II trials of the same drug are sometimes conducted in patients with several different types of cancer to determine if the therapy is likely to be of benefit in treating more than one tumour type. These trials also help establish the optimum dose, identify short-term side effects and explore whether there are likely to be any potential safety problems associated with the drug. Patients in phase II trials usually have refractory disease, and must have measurable disease so that the response to the investigational treatment can be monitored. Phase II studies can take from six months to two years to complete.

Phase III trials usually compare a new drug with current standard therapy in large matched groups of patients (i.e. in large, randomized trials). Information on the overall risk–benefit relationship of the investigational drug that provides evidence to support its use in a specific indication (i.e. to treat a specific disease in a specific group of people) is gathered during these trials. This enables clear prescribing information to be developed. Phase III trials can take one to four years to complete, depending on the disease.

Phase IV trials continue after the drug has been approved to test for further side effects as well as exploring using different treatment regimens for the drug in a particular cancer (also called therapy optimisation studies), or in specific patient populations. Phase IV studies can continue for many years.

**Figure 4**: Getting a drug from the bench to the bedside
Clinical trial design

Clinical trials on drugs are performed according to Good Clinical Practice (GCP) standards. GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve human subjects. Clinical trials carried out according to GCP standards ensure that the rights, integrity and confidentiality of trial subjects are protected. Before a trial begins, researchers prepare a protocol according to GCP standards that describes: the study aims; what types of people may
or may not participate in the trial; the schedule of tests, procedures, medications, and dosages; and the length of the study.

Trials can be carried out at more than one site (called a multicentre trial). Multicentre trials are conducted according to a single protocol but carried out by more than one investigator.

Later-stage clinical trials are designed very carefully to make sure that the results are due to the treatment under study and not due to chance. In order to reduce this risk the drug is given to one group of patients with a disease (the experimental arm) and the outcomes are compared with a similar group of patients who have not been given the drug (the control arm). This is called a controlled trial. Patients in the control arm may be given a placebo – an inert “dummy” tablet or injection that looks similar to the drug under investigation. This is called a placebo-controlled trial.

Placebo-controlled trials are necessary because, for a number of reasons, people taking “medications” that are actually inactive often experience improvements in their condition. However, people with cancer are unlikely to find themselves in a placebo-controlled trial for several reasons. Firstly, cancer treatments tend to have numerous side effects, so people taking the placebo would quickly be able to work out which arm they were in. Secondly, and more importantly, it would be unethical to deprive someone with a life-threatening disease of the best available treatment.

Placebos can also be used in cancer trials as way of assessing whether a new drug is an improvement over standard treatment. The patients in the control arm of the trial are given standard treatment plus placebo, while those in the “test” arm are given standard treatment plus the new drug X.

This is known as an active-control clinical trial, because even people assigned to the control group receive an active treatment.

Figure 5: A simple form of active trial design for a cancer drug
Placebos may occasionally be used in trials involving the small number of cancers with no other appropriate treatment options; however, in these circumstances the investigational agent is more often compared with best supportive care (treatment that will improve comfort and quality of life) rather than a placebo.

Trials may have more than two arms and compare different combinations of drug schedules and doses.

As it is important to make sure that people participating in a trial are broadly similar, the researchers will establish criteria to define who can or cannot participate in the trial. These are called eligibility criteria, and may include age, gender, cancer type and stage, medical history and current health status. There are generally two sets of criteria: inclusion criteria, which define who may take part in the trial, and exclusion criteria, which define who is not eligible to take part.

In clinical trials that compare two or more treatments, participants have no choice about which arm of the study they are assigned. Neither do the doctors, the researchers or the trial sponsor. Instead, participants are randomly assigned to different arms of the trial; normally this is done by computer. This process is called randomisation. Randomisation helps ensure that the distribution of patients between each arm is equal and therefore the arms are matched in terms of age, gender and stage of disease. Patients have an equal chance of being assigned to either arm of the trial. Like should only be compared with like, and having the same number of people with similar characteristics in each arm ensures that the comparison between the two arms is fair. Sometimes it is necessary to break down the cohorts further to study the impact of the drug on different groups (e.g. according to age, disease stage, ethnic group etc.). This is called stratification.

There is a risk of bias if participants or researchers know to which arm of the trial the patient has been assigned. This can be prevented by “blinding” the study; code numbers are assigned to each individual instead of patient names, which treatment arm they are assigned to is not revealed and therefore no-one knows whether any given patient is getting the investigational or standard treatment. A study is called a double-blind trial when both healthcare professional and patients are “blind” to which treatment is being given. However, sometimes the nature of the drug means that it is necessary for the doctors to know who is receiving the trial drug right from the outset of the trial – this is called a single-blind trial, because, although the doctors know, the patient is not told which drug they are taking.

It can be quite difficult to conceal from people which treatment participants are receiving. It is relatively simple to do this if both the experimental and standard treatment involves simple medications that are administered at regular times during the day. In this case both treatments will be designed to look alike and instead of putting the names of the medications on the labels, a code will be used. Neither the patient nor the research team will know which medication they are receiving until the code is broken at the end of the study. Placebos, where used, are always matched in appearance and route of administration to the active drug to maintain blindness. However, if the treatments being compared are more complex and very different from each other, it will be near impossible to “blind” participants and the research team. Trials that cannot be blinded are called open-label trials and are used quite commonly in cancer research.

**How are patients’ rights protected during clinical trials?**

Before a clinical trial commences, the protocol has to undergo stringent appraisal by different groups including the national regulatory agencies or health authorities and ethics committees/Institutional Review Boards. The guiding principles for clinical trial design and ethical review are embodied in the Declaration of Helsinki. This declaration was drawn up in 1964 by the World Medical Association as a statement of ethical principles to provide guidance to physicians and other participants in medical research.
Involving human subjects, and it has been periodically reviewed and revised. It states that medical progress is based on research which ultimately must rest in part on experimentation on human subjects, and that in medical research on human subjects, considerations related to the well being of the human subject should take precedence over the interests of science and society.

Ethics committees are usually local to the institutions where the research is to be conducted. They comprise doctors, nurses and other healthcare professionals as well as lay members of the public. Researchers have to present to the committee a justification of why the research needs to be carried out, together with information on how it will be conducted, which patients will be involved, what will be done to them and why, and what steps will be taken to inform patients about the research and obtain their consent. The investigators will also have to demonstrate that they are suitably qualified and appropriate people to carry out the research and interpret the findings.

When the study has commenced, researchers are obliged to inform the supervising authorities of any problems that arise during the clinical trial. Trials will be stopped if the risks involved outweigh the benefits for patients.

Patients must consent to take part in the trial. Informed consent is a process by which patients are provided with extensive explanation and information about the trial so that they can make an informed decision about whether or not to participate. The principles of informed consent are embodied in the Nuremberg Code which provides guidance and a framework to which all clinical trial informed consent procedures should adhere.

Specifically, patients should be provided with details about the purpose of the study, the tests and other procedures used in the study, and the possible risks and benefits. It is crucial that patient entry into the clinical trial is entirely voluntary. Patients who agree to take part in the study are asked to sign the informed consent form. However, signing the form does not mean people must stay in the study. People can leave the study at any time – either before the study starts or at any time during the study or the follow-up period. If people do not enter the trial, or choose to leave once they have started, it will not stop or interfere in any way with them receiving appropriate treatment.

A data and safety monitoring plan is normally developed for the clinical trial, and for phase III trials a Data and Safety Monitoring Board (DSMB) is established. The DSMB is an independent committee that has the responsibility of ensuring that the risks of participation continue to be acceptable. They review data at different points during a trial and will stop a trial if safety concerns arise or when the trial’s objectives have been met. The DSMB also make recommendations about modifying the trial.

A recent example of a DSMB stopping a study because of safety concerns was a phase III trial of a monoclonal antibody in combination with other drugs in advanced colorectal cancer, which was stopped after the deaths of four patients in one arm of the trial. DSMBs will also stop a study if one treatment proves to be significantly superior to the others during the course of the study and therefore it would be unethical not to offer trial participants the opportunity to transfer to the better treatment. This happened recently with the trials of trastuzumab (Herceptin) in the adjuvant setting. The decision to halt a trial early is not without controversy, since important information about a drug's/regimen's efficacy and safety can no longer be gathered, particularly in relation to survival and long-term side effects.
Monitoring during clinical trials

During the clinical trial, participants are closely monitored to determine the safety and effectiveness of the treatment under investigation. Patients in clinical trials often have to undergo more consultations and examinations than usual because a lot of information needs to be collected about their disease and progress and there must be very careful monitoring of the impact of the drug in terms of side effects. Information about the drug’s pharmacokinetics or pharmacodynamics also needs to be collected, which means the patients often have to give extra blood/tissue samples.

At the start of a trial, the sponsor (i.e. the pharmaceutical company or academic institution that is conducting the trial) must prepare an Investigators Brochure, which summarises the available important information about the drug and details of whom to contact if any problems occur during the trial. Whilst the trial is underway, investigators are obliged to report a serious adverse event associated with the investigational drug within 7 days of its occurrence if the event was fatal, life-threatening or unexpected, and within 15 days if the event was serious but not fatal or life-threatening.

How do we measure clinical trial outcomes?

Each trial has a pre-specified goal or endpoint. The endpoint chosen for a particular trial depends on the phase of the trial and the type of disease and/or agent under investigation. The endpoints must be clearly defined before the trial begins. Endpoints commonly used in cancer clinical trials include:

- Overall survival
- Disease-free survival
- Progression-free survival
- Objective response rate
- Time to progression
- Symptom control
- Quality of life
- Tolerability

These endpoints can be used to demonstrate the efficacy or safety/tolerability of a drug.

Efficacy endpoints

Overall survival is a measure of the trial participants who are still living at the time of follow-up. It is often regarded as the “gold standard” of endpoints. However this endpoint can suffer from a dilution effect, which may occur due to crossover or use of further lines of therapy because of disease progression. Crossover is when a patient fails to respond to treatment in one arm and they are allowed to cross over to the other treatment arm. This can confound the assessment of survival.

Some argue that the use of overall survival as an endpoint is unethical and impractical for some cancers (e.g. indolent cancers that do not grow rapidly), particularly if it results in trial protocols that do not include crossover provisions. Other dilution factors include different responses in different sub-groups of patients, so the ability to pick out the high-responders is diluted. Studies designed to demonstrate an impact of a treatment on overall survival need large samples and a long follow-up time. For highly treatable cancers it may take many years to obtain enough data to demonstrate overall survival.

For these reasons, other survival endpoints are often used as primary endpoints in clinical trials. Disease free survival (DFS) is the length of time following treatment that the patient survives without evidence of detectable disease. Progression free survival (PFS) is a measure of how long the patient lives without any worsening of their disease. The only difference between PFS and time to progression (another endpoint that is explained later) is that death is included in the measure of PFS. Since progression free survival or disease free survival are good predictors of overall survival they are often used as a primary endpoints in cancer clinical trials. The advantage of using these endpoints is that there is no dilution effect, and the follow-up time is much less. However, there is a
greater potential for bias because of variability can occur when assessing progression.

Some trials use endpoints to measure objectively the tumour’s response to an investigational treatment. Response endpoints include response rate, time to progression (TTP) and symptom control.

Response rate is a measure of whether the tumour responds and shrinks in size during treatment. The investigative agent may induce a complete response (CR), partial response (PR) or stable disease. CR is where no trace of detectable disease remains. This does not equate to a "cure," (since the tumour may regrow or metastases may subsequently appear) although some patients with a CR may be "cured". Partial response is where there is a post treatment decrease in the size of a measurable tumour of at least 50% of the total cross section (the area of the tumour that would be seen if the tumour could be cut in half). Stable disease describes the situation where there is no measurable response. The investigative agent may also be ineffective and the disease may progress. With disease progression the tumour continues to grow or additional tumours appear.

Response may also be assessed by measuring pre-defined response biomarkers (do not confuse these types of biomarkers with the predictive biomarkers that are used to assess patients for suitability for targeted therapies, see page 35). Biomarkers of response may be molecular markers or biochemical parameters that show that a tumour is decreasing in proliferative activity, there is increasing apoptosis, or there are other biological changes that can be shown to have an anti-tumour effect. They can be measured using a variety of laboratory or imaging methods.

The degree of response to treatment is normally categorised according to international standards which are applied consistently. For example the RECIST (Response Evaluation Criteria in Solid Tumours) is used as a means of measuring how solid tumours respond to treatment with an investigational drug.

These criteria have been very useful but may not be so applicable to evaluating targeted therapies that are cytostatic rather than cytotoxic.

Because of the limitations associated with response rate as an endpoint, other endpoints such as symptom control (patients’ own reports of how they feel and their symptoms) are used to provide additional evidence of clinical benefit. Symptom control is an important patient reported outcome, but is an imperfect endpoint because of measurement difficulties, and the subjective nature or individual reporting of symptoms.

Since a tumour may initially respond to therapy but then start to grow again, the duration of response is at least as important as response rate. Short lived responses are unlikely to be of benefit for patients, particularly those with few symptoms and where the investigational agent is associated with a burdensome treatment schedule and side effects. Duration of response is measured by the time to progression (TTP) endpoint. TTP is the time from randomization to documentation of progressive disease based on tumour dimensions.

However, TTP is limited because it is, at best, an estimate of when the actual disease progression occurs, since this can happen at any point between the scheduled clinic visits when the assessments are carried out. TTP can vary based on frequency of observation therefore both (or all) arms of a randomised trial must have the same schedule of disease assessment.

Many Phase III trials compare "Quality of Life" (QOL) outcomes between the different treatments. QOL is assessed using standardized questionnaires which ask the patient subjective questions about how they are feeling and functioning. Assessment of QOL can be helpful in demonstrating the balance between the burden of side effects and the efficacy of treatment.
Safety and tolerability endpoints

Measurements of toxicity enable side effects associated with an investigational drug to be identified. Although the details will vary with the precise nature of the side effect, some type of numeric scale is used to rate the severity of the toxicities. Each side effect is separately rated from 0 to 4. A rating of 0 = side effect not present; 1 = present but minor; 2 = present, with moderate effect; 3 = present, with significant effect; and 4 = potentially life-threatening effect. If the patient experiences grade 3 or 4 toxicity, further treatment is often delayed or even stopped; thereby compromising the potential outcome of treatment.

In the early trial phases, measurements of toxicity will enable the dose-limiting toxicity of a drug to be established. In later phases, toxicity measurements are used to look at the longer-term impact of the investigational drug on organ function. This will enable decisions to be made about the drug’s contraindications, interactions and monitoring requirements.

Contraindications are a list of criteria that should exclude a patient from being prescribed the drug in question. For example, if the drug can cause heart problems, it is contraindicated for patients with existing cardiac disease.

Toxicity measurements are used to determine both the short-term and longer-term impact of a drug on organ function.

The contraindications form part of the drug label or prescribing information. The drug label has to be approved during the licensing process. It also contains warnings and precautions that give the physician more detailed information about using the drug in particular patient groups, for example, which drugs cannot be given to children or breastfeeding women. Interactions are potential reactions between different drugs that the patient may be taking at the same time and monitoring requirements are the examinations or tests that must be performed while the person is taking the drug to ensure that no harmful effects are occurring.

How do we decide that a trial has had a successful outcome?

Success is a complex issue in drug trials, because while we are ultimately looking to find a drug that is better than the current “standard” treatment in terms of efficacy, it is also acceptable to develop a drug that has a better safety profile or is easier to administer than the standard.

Success is a complex issue in drug trials. Cancer clinical trials often have several measures of outcome.

Clinical trials in cancer often have several measures of outcome such as recurrence of disease, survival and toxicity. Normally a trial will have only one primary endpoint as well as a number of secondary endpoints. The trial will be deemed successful if it has achieved its primary endpoint. The impact of the agent on secondary endpoints can provide support for the benefit of a new treatment.

To demonstrate the effectiveness of a new agent, clinical benefit needs to be shown in a defined group of patients. Benefit may mean a longer time free from worsening (progression) of the cancer or a longer survival time. These kinds of benefits are established in superiority trials where the new drug is compared to standard treatment. Sometimes benefit may come in the form of less serious side effects or better QOL than standard treatment, without any important decrease in the
length of time free from worsening of the cancer or in survival time. These kinds of benefits are established in **non-inferiority trials**, where the new drug is compared to the standard, with the aim being to show better tolerability and possibly QOL for the new drug, but no important difference in survival time.

Cancers rarely disappear spontaneously and therefore it is reasonable to assume that tumour regression after treatment can be attributed to the effects of the treatment. Thus, response rate can act as a **surrogate endpoint** that is reasonably likely to predict true clinical benefit (i.e. how the patient feels, functions or survives). For response rate to be a valid surrogate endpoint, the response seen must have a direct link with the biological action of the investigational drug. For example, haematological and cytogenic responses (i.e. blood and other cell responses) were used as surrogate endpoints to demonstrate the effectiveness of imatinib (a treatment for leukaemia) long before evidence on survival became available. However, it is very difficult to be sure an endpoint is really a surrogate – so while there is a lot of work in progress to try to find new surrogate endpoints that may speed up the development of new drugs for cancer, the process will still take a long time.

**Sometimes clinical benefit may come in the form of less serious side effects or better quality of life.**

Because molecular targeted therapies are cytostatic rather than cytotoxic, it is more likely that stable disease or a small reduction in tumour bulk will be seen with these agents than with other therapies. Therefore, medical imaging techniques are less valuable in demonstrating the effectiveness of these therapies. Some haematological or molecular markers can act as surrogates to show the effect of a particular therapy on a target of interest. However, there is a need to define and validate surrogate markers that can show both the effect and clinical benefit of targeted therapies.
Chapter 2: Regulating Cancer Drugs
Why regulate cancer drugs?

Regulation of cancer drugs enables us to protect patients from harmful drugs while at the same time ensuring that patients have access to high quality, and effective treatments. Drug approval is really based on satisfying regulatory agencies that the therapeutic benefit of the drug in question outweighs the disadvantages of any side effects. Once approved, drugs must also continue to be monitored. The legislation regulating drug approval is complex, constantly evolving and difficult even for experts to understand!

Who are the regulators?

Regulation of all drugs is under the control of regulatory agencies and each country has its own agency. Some of the main agencies are outlined in Table 2. This booklet outlines the process, using the European and US systems to illustrate the procedures. This is not to ignore the processes in other countries, but they are too numerous to mention.

Although there are regulatory agencies in each European country, a centralised co-ordinating agency, called the European Medicines Agency (EMEA) was established in the European Union in 1995. The EMEA co-ordinates a network of regulatory agencies in the 25 Member States of the European Union plus the 3 EEA/EFTA States (Iceland, Lichtenstein and Norway). All applications for the approval of cancer drugs in Europe must be submitted via the EMEA’s centralised procedure. The EMEA itself does not assess applications for marketing approval – they are sent to assessors in two of the regulatory agencies in the network, called rapporteurs and co-rapporteurs (e.g. the UK Medicines and Healthcare products Regulatory Agency (MHRA), the French Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSPS), etc.). The assessors then present their findings to a committee made up of representatives from all the Member States who will make a recommendation to the European Commission as to whether the agent should be approved (this committee is called the Committee for Human Medicinal Products – CHMP). At the end of this process, if approval is given, the pharmaceutical company will be granted an authorisation to market the drug for a specific indication in all 28 countries served by EMEA.

A drug will be approved once a regulatory agency is satisfied that the positive benefits outweigh its disadvantages.

An increasing number of programmes have been introduced to enhance co-operation between

Table 2: Some of the major Regulatory Agencies responsible for granting marketing authorisation for drugs

<table>
<thead>
<tr>
<th>Australia:</th>
<th>Therapeutics Goods Administration (TGA)</th>
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<tbody>
<tr>
<td>Canada:</td>
<td>Therapeutic Products Directorate (TPD) of Health Canada</td>
</tr>
<tr>
<td>European Union and EEA-EFTA States:</td>
<td>European Medicines Agency (EMEA)</td>
</tr>
<tr>
<td>Japan:</td>
<td>Ministry of Health Labour and Welfare (MHLW)</td>
</tr>
<tr>
<td>Switzerland:</td>
<td>Swissmedic – Schweizerisches Heilmittelinstitut</td>
</tr>
<tr>
<td>United States:</td>
<td>Food and Drug Administration (FDA)</td>
</tr>
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different regulatory agencies. For example, the FDA and EMEA have started to provide parallel scientific advice in order to facilitate the development of safe and effective medicines. The agencies have also started to share information about the safety profiles of different products. The two agencies hold regular meetings to discuss guidelines relating to cancer drug approval processes as well as the approval of individual cancer drugs.

In an effort to harmonise the regulation of drugs worldwide a number of regulatory agencies, along with experts from the pharmaceutical industry, meet to discuss scientific and technical aspects of drug regulation. These meetings are held under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals (also known as ICH). ICH meetings result in recommendations on ways to achieve greater harmonisation in the interpretation and application of technical guidelines and requirements for the approval of drugs, with the ultimate aim of reducing unnecessary testing and eradicating delays in the research and development of new drugs. ICH guidelines form the basis of many of the procedures used by regulatory agencies worldwide.

**What advice do pharmaceutical companies get from regulators?**

Pharmaceutical companies often seek advice from regulatory agencies when planning clinical trials, to ensure that their drug development plans are appropriate. Companies that secure advice from regulators are more likely to find their development is acceptable to the licensing authority. The timing and extent to which the regulatory agencies provide facilities for consultation varies between countries.
Drug review process

What procedures are used to evaluate a drug for approval?

Procedures for drug review vary between countries, but they basically follow similar pathways to approve drugs. Details of the procedures in the EMEA, and FDA are given in Appendices I and 2.

In order to gain approval for a drug, the pharmaceutical company, as future manufacturer of the medicinal product, is required to apply for marketing authorisation. This involves submission of a dossier containing documentation which consists of information about preclinical and clinical data to show the safety and efficacy of the product, a chemical-pharmaceutical dossier for quality information as well as details about dosing and the proposed labelling for the new product. Companies also have to submit information about how the medicinal product is manufactured and what controls are in place to ensure that the product will be manufactured to a consistently high quality. Manufacturing plants also need a manufacturing authorisation to produce drugs.

Regulatory agencies assess the dossier to determine whether the new drug is both effective and safe to be used in a particular population of patients. When the licensing authority is satisfied that the drug is effective and safe (i.e. benefits outweigh possible side effects) a drug is granted marketing authorisation (sometimes called a licence).

What evidence do the regulators look for?

When reviewing drugs, regulators must seek answers to a number of questions:

- Is the drug effective?
  - Has the drug had an impact on patient overall survival? (if this is a feasible endpoint)
  - Does the drug improve patients’ quality of life even if it does not cure their disease? (i.e. improves physical function, helps the patient feel better or controls symptoms)
  - Did the study include enough participants to be able to determine that the drug works effectively?
- What are the drug’s side effects?
  - Is the drug’s efficacy sufficient to make these side effects acceptable?
  - What special precautions need to be taken to minimise side effects?

In general regulators examine the application to make sure that the new drug has an acceptable safety profile and its efficacy has been demonstrated in a number of well-controlled clinical trials. The regulators will assess the data to make sure that enough evidence has been supplied to support the drug’s use in a particular patient population, and for a specific type and stage of cancer (e.g. advanced cancer or adjuvant treatment, etc.). Most drugs are approved initially for the treatment of advanced cancer.

Regulators will look at both the short- and long-term safety profile of the drug. Clearly a new drug with a low risk of acute, reversible side effects but high risk of long-term, irreversible complications will be viewed differently to one with a low risk of short- and long-term toxicity. This is particularly important in the evaluation of molecular targeted therapies, where it is probable that patients will have to remain on treatment for a long period of time.

As mentioned previously, all clinical trials need to have a pre-defined efficacy endpoint. Regulators will look to see if the trials supporting the application have achieved their primary endpoint and whether the secondary endpoints provide additional evidence of the agent’s efficacy. Drugs are rarely approved if the primary endpoint has been missed, even when the drug has been shown to be effective on a number of secondary endpoints. A company would have to provide a reasonable explanation for missing the primary endpoint (e.g. crossover rate was very high) and robust evidence for the drug’s efficacy on secondary endpoints.
Regulators may occasionally accept the initial results from non-comparator studies (i.e. single-arm studies) that are carried out in previously treated patients with no other established treatment options, but only if outstanding activity has been demonstrated against the tumour and the overall results indicate a positive risk–benefit profile for the product.

Sometimes regulators will approve a drug based on the effect of a drug on a surrogate endpoint (see page 29). Surrogate endpoints are only accepted when the need for the drug is so great that it would be unacceptable to delay approval until the information needed to demonstrate an effect of the drug on prolonging life (i.e. overall survival) has been collected. If a drug is approved in these circumstances the regulators normally ask the company to continue to collect further information to demonstrate the effect of the drug on survival. Approval of a drug on the basis of surrogate endpoints is fairly common in the cancer setting because of the life-threatening nature of the disease and cancer patients cannot afford this delay.

This approach is not without its problems, particularly with targeted therapies. For example, a new therapy was developed that showed excellent results in preclinical studies and encouraging results in early studies. Some patients showed tremendous responses to the drug with marked tumour shrinkage. This led to early licensing of the drug in the US. However, phase III studies of the drug failed to show an impact on long-term survival in a broad population of patients with a particular cancer. This was unexpected and disappointing.

Further analysis of sub-groups of patients, however, showed that there was a small, but clearly definable, group of patients in whom the drug worked very well indeed. This has shown that in using targeted therapies, we are still learning about how to identify the patients who stand to benefit most from a new therapy.

Regulators are now very keen on researchers identifying the group of patients who are most likely to respond to the experimental drug in question, before they submit the licence application. This requires identifying some form of predictive biomarker, which differentiates patients who will, from those who won’t, respond (do not confuse these with response biomarkers, see page 27). Predictive biomarkers can include parameters such as age, number of previous drug treatments or smoking status. However, ideally they are biomarkers, biological markers which are indicators of the patient’s genetic make-up and shows whether the patient actually possesses the aberrant gene or pathway that is being targeted by the new therapy.

For some therapies, a validated biomarker for the drug target may not be available, but there are others where the biomarker has been clearly identified. A good example is trastuzumab (Herceptin) which targets the HER2 receptor. HER-2 testing of women with breast cancer makes it easier to identify the sub-group of patients whose tumours have a specific molecular make-up - the presence of HER2 receptor – that makes them more likely to respond to trastuzumab. If trastuzumab had been tested in all women with breast cancer, the results of the trials would have been less positive because they would have been diluted by including all breast cancer sub-types, many of which do not respond to this drug. The challenge is to identify which tumours will respond to a specific therapy and develop a simple test to measure the likelihood of response.
Who provides regulatory agencies with advice?

Regulatory agencies have access to special advisory groups that provide guidance as to whether a cancer drug should be approved. For example the FDA seeks guidance on the approval of cancer drugs from the Oncology Drug Advisory Committee (ODAC). ODAC meetings take place in public and can be attended by anyone with an interest in the topics under discussion. In Europe a Scientific Advisory Group – Oncology (SAG-O) provides the CHMP with guidance on the approvability of cancer drugs. Unlike ODAC meetings, SAG-O meetings are held in private and, as yet, there is no patient representation on the Group. In an effort to increase transparency a list of the SAG-O members is now available on the EMEA website. Currently ODAC is the only advisory committee with patient representation. It is important to note that regulators are not bound by the advice given by advisory committees.

What does regulatory approval mean?

When a drug is given a marketing authorisation, it is licensed for very specific conditions and for use in specific groups of people – the indication. The regulators will also approve a document that summarises all the known information about the drug, including: which patients can receive the drug; for which indication(s); how often the drug should be taken; what are the contraindications and side effects; and what monitoring is required. In Europe this is called the Summary of medicinal Product Characteristics (SmPC), and in the US it is Proposed Package Insert (PPI). The pharmaceutical company may only market the product according to the information laid down in this document.

A Patient Information Leaflet (PIL) and the label for the drug packaging must also be approved by the regulatory agency.

These documents often vary across agencies because regulatory agencies have differing requirements, and companies must negotiate the final version of prescribing information with each agency. This means that there can be significant variations in indications for the same drug in different countries. For example, cetuximab is approved for the treatment of metastatic colorectal cancer in both the US and Europe. However, in Europe the agent is approved for use only in combination with irinotecan (a chemotherapy drug), while in the US it is indicated expressly for EGFR-expressing (a biomarker) metastatic colorectal cancer, and may be used in combination with irinotecan or as a single agent for patients who are refractory to irinotecan-based therapy.

How long does it take to approve drugs?

Timelines for the review of applications are laid down in the legislation governing pharmaceuticals in different countries. For example, in the US the FDA must make a decision within 12 months on a regular application and within 6 months in the case of applications designated for priority review. In Europe the CHMP must give its opinion within 210 days – this is followed by a decision-making phase that can take up to three months. Sometimes the regulators require extra information in order to make a decision on the safety and efficacy of a new agent, and ask the company to supply this information. The clock is stopped during the time it takes the company to gather and submit the information (so-called clock-stop time). Once the scientific decision to license a drug has been made, a bureaucratic phase follows that can take up to 3 months.

There are significant differences in the time it takes regulators in different countries to approve cancer drugs (see Table 3 ). A number of reasons contribute to this unsatisfactory situation – for example the FDA is much more likely to progress promising drugs more rapidly through the approval system. A major contributing factor to the differences in timelines
between the US and Europe is the post-approval procedure which is more bureaucratic in Europe. This means that, in general, US patients gain access to promising drugs more rapidly than their counterparts in other countries.

**Rapid processing of applications for promising cancer drugs**

All regulatory agencies have procedures in place for making sure that patients receive drugs that are particularly promising and will have significant public health benefits as soon as possible. There are two key processes for making sure that patients receive important drugs in a timely manner – rapid assessment and conditional approval.

**Rapid review procedures**

The drugs that are eligible for rapid assessment are those that are intended to treat serious or life-threatening conditions or have the potential to address unmet needs (e.g. where there is currently no effective treatment). The classification does not apply to a product alone, but encompasses the product and the specific indication for which it is being studied. For example, the application may be for new drug A in lung cancer. Again the exact procedures may vary slightly between regulatory agencies, but the principles are the same. Essentially, the review process is as stringent as usual, but a particularly promising drug is progressed more quickly. Some regulatory agencies (e.g. in the US and Europe) are obliged by law to carry out the rapid assessment within a certain timeframe. In the US this process is called “priority review” and in Europe “accelerated assessment”. In other countries the agencies are merely required to review the applications “as soon as possible”.

### Table 3: Difference in approval times between EMEA and FDA for selected targeted therapies since 2001

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Brand name</th>
<th>EU filing date</th>
<th>Approval time (days)</th>
<th>US filing date</th>
<th>Approval time (days)</th>
<th>Difference in access time</th>
</tr>
</thead>
<tbody>
<tr>
<td>imatinib</td>
<td>Glivec (Gleevec)</td>
<td>27/02/01</td>
<td>253</td>
<td>27/02/01</td>
<td>72</td>
<td>5 months</td>
</tr>
<tr>
<td>bortezomib</td>
<td>Velcade</td>
<td>04/02/03</td>
<td>446</td>
<td>22/01/03</td>
<td>111</td>
<td>11 months</td>
</tr>
<tr>
<td>cetuximab</td>
<td>Erbitux</td>
<td>30/06/03</td>
<td>364</td>
<td>14/08/03</td>
<td>182</td>
<td>4.5 months</td>
</tr>
<tr>
<td>bevacizumab</td>
<td>Avastin</td>
<td>05/12/03</td>
<td>403</td>
<td>29/09/03</td>
<td>151</td>
<td>10 months</td>
</tr>
<tr>
<td>erlotinib</td>
<td>Tarceva</td>
<td>26/08/04</td>
<td>389</td>
<td>02/08/04</td>
<td>108</td>
<td>10 months</td>
</tr>
<tr>
<td>sorafenib</td>
<td>Nexavar</td>
<td>28/09/05</td>
<td>297</td>
<td>11/07/05</td>
<td>162</td>
<td>4.5 months</td>
</tr>
<tr>
<td>sunitinib</td>
<td>Sutent</td>
<td>28/09/05</td>
<td>301</td>
<td>10/08/05</td>
<td>148</td>
<td>5 months</td>
</tr>
<tr>
<td>dasatanib</td>
<td>Sprycel</td>
<td>Jan 06</td>
<td>Not yet approved</td>
<td>28/12/05</td>
<td>182</td>
<td>?</td>
</tr>
</tbody>
</table>

All of these drugs were assessed under the priority review procedure in the US; only Glivec was given rapid review in Europe.
Approval with conditions attached

Regulatory agencies normally only approve cancer drugs based on the results from double-blind, randomised, comparative, phase III trials. However, there are processes that allow approval to be granted on the basis of phase II studies in certain, well defined, situations. Approval in this context is based on evidence of the drug’s activity on surrogate endpoints (see previous discussion on endpoints). A fundamental component of this process is that the company must continue testing after approval in order to demonstrate that the drug provides therapeutic benefit to the patient. So in effect the approval is coming earlier on in the process of collecting the full dossier of information on the drug, but the sponsor is still collecting evidence to complete the drug’s dossier, even though this occurs after approval. Conditional approval procedures vary across regulatory agencies, as does the terminology used for the procedure. It is called “conditional marketing approval” in Europe and “accelerated approval” in the US. In Europe this procedure came into force in April 2006, and the cancer drug sunitinib (Sutent) was the first drug to be given a positive opinion through the conditional approval procedure.

Other procedures for ensuring timely approval of new drugs

The FDA also uses another type of fast-track procedure to facilitate the development and expedite the review of new drugs that are intended to treat serious or life-threatening conditions and that demonstrate the potential to address unmet medical need. This works by the pharmaceutical company having regular meetings to seek FDA’s input into clinical development plans as they progress and reaching early agreement on the design of the major clinical efficacy studies that will be needed to support approval.

The company also has the option of submitting the marketing authorisation application in sections rather than all components simultaneously (called rolling submission), and the option of requesting evaluation of studies using surrogate endpoints. The FDA is therefore well acquainted with the study before the licence application is submitted and the company has ensured that it is aware of any FDA concerns and can address them as studies proceed. The fast-track designation does not necessarily lead to priority review or accelerated approval.

In Europe, there is yet a further system for approving drugs under “exceptional circumstances” – this is different to conditional approval in that exceptional circumstances authorisations do not lead to the completion of a full dossier and a “normal” marketing authorisation.

Under the exceptional circumstances system, drugs can be granted a licence even though comprehensive information about that drug is not available, so long as that information is deemed to be unobtainable.

The reasons accepted for the information being unobtainable are closely defined and include:

- the condition is so rare that the investigators cannot possibly hope to recruit sufficient patients into clinical trials within a sensible time period
- the present state of scientific information prevents comprehensive information being obtained
- it would be medically unethical to collect such information (e.g. submitting seriously ill people to extensive tests)

In such cases, marketing authorisation may be based on phase II studies alone, or the clinical trial may be an uncontrolled trial when then there is no approved treatment available to act as a comparator and the drug shows outstanding anticancer activity. In this situation approval is often based on surrogate endpoints. Exceptional circumstances authorisations are reviewed annually to reassess the risk–benefit balance.

Applications for new indications for approved drugs

Once experience has been gained with the drug in a particular setting the manufacturer may decide to
apply for an extension of the groups of patients in whom the drug can be used, based on the results from further clinical trials. For example, a drug that was initially licensed for use in the advanced setting may also be effective in early disease, or there may be a tumour type that responds well to the drug in addition to the tumour type for which it is licensed, or it may also be suitable for children.

Applications for a new indication must be accompanied by robust evidence to demonstrate that the drug has significant activity for the specific disease, patient population and stage of disease. The regulators will weigh up the risk–benefit balance of using the drug for the new indication, even if there is well-established evidence of its safety and efficacy in the initial indication. This is because the risk–benefit ratio for cancer drugs varies across different diseases, patient populations and stages of disease. For instance, a drug may have an acceptable safety profile when used in the treatment of patients with advanced cancer, but not in situations of far lower risk, such as in the adjuvant setting or as a preventative agent, where a large number of healthy people are exposed to the treatment and only a small number will obtain benefit. A higher degree of risk may also be acceptable in a drug that will be used for the treatment of a cancer with few other treatment options. Acceptable risk may be evaluated differently in children, who have to live with the side effects for their entire lives, than in adults; the drug could also affect the process of their development.

Drugs for rare cancers

Many types of cancers are rare conditions (see Appendix 3) and researchers face problems in finding drugs that are active against these cancers because often there are not sufficient people in whom the effects of drugs can be investigated. Over the past decade it has also become clear that developing drugs for small numbers of users is not always commercially viable. Given that the investment required to develop a drug is enormous, manufacturers are often unable to recoup their investments when developing drugs for rare diseases and therefore they may be deterred from pursuing the development of these drugs. Consequently, governments have made a number financial and market protection concessions available to motivate companies to develop drugs for rare diseases, while at the same time protecting established standards of safety and efficacy. This is orphan drug designation.

Orphan drugs designation

Orphan drugs are defined as those that are used to treat an illness or condition that affects very small numbers of people (defined in the EU as a prevalence of not more than 5 in 10,000 persons, and in the US as less than a total of 20,000 people).

To obtain orphan drug designation, manufacturers need to submit an application to the relevant regulatory agency for any drug in development that they believe should qualify for orphan status. Orphan drug designation does not guarantee that the drug will be ultimately approved – it is just a system that provides financial and marketing exclusivity benefits to motivate companies to invest in the development of drugs for rare conditions.

Despite the problems of finding sufficient patients with rare cancers in a reasonable time frame, the opportunity of securing orphan drug designation for a cancer indication means that more and more companies are starting to develop compounds targeted at these cancers. At the time of writing (June 2006), some 140 drugs, either new entities or modifications of existing drugs, had received orphan designation for a cancer indication in Europe. Few of these drugs have been approved because they are still in development or, perhaps, have failed to pass a key passage in the development process.
Patient involvement in the regulation of cancer drugs

The role of regulatory authorities is to protect the public from unsafe medicinal products, and regulators must decide how to balance the risks with the benefits of a specific drug. With life-threatening diseases it may be more acceptable to licence a drug with a higher level of risk than would be acceptable for a less serious condition, because so much more is at stake. Since it is the cancer patients themselves who ultimately take the risk of experiencing adverse events, and also potentially gaining the benefits from a specific drug, it is clear that they should be consulted about the risk–benefit ratio of drugs under evaluation. This is important, since people will interpret risks very differently depending on their situation, and a regulator may not understand the degree to which patients are willing to trade risks off against benefits, particularly when they have run out of treatment options. Some agencies consult with patients to help them make an appropriate decision on the risk–benefit balance; however, the extent to which regulators do this varies hugely across agencies.

Since it is cancer patients who ultimately take the risk of experiencing adverse effects and potentially gaining the benefit of a new drug, they should be consulted about the risk-benefit ratio of the drug.
In the US, the FDA has a Cancer Liaison Program which includes a process for recommending, recruiting and training patient representatives to serve on cancer-related advisory committees such as the Oncology Drug Advisory Committee (ODAC). ODAC has a consumer representative who is appointed for the same term as the other committee members, and has the same voting rights. The committee also co-opts one other lay person, who has experience of the disease in question, as each new drug is considered. The FDA has also established a Cancer Drug Development Patient Consultant Program, which has the goal of incorporating the patient perspective into the drug development process. This programme provides cancer patient advocates with the opportunity to participate in the FDA drug review process. Patients serve as consultants in the pre-approval and clinical trial phase of cancer drug development and advise the FDA and drug sponsor on topics such as clinical trial design, endpoint determination, expanded access protocol development, and clinical trial patient recruitment strategies.

Some examples of EMEA activities in which patients’ and consumers’ organisations may be involved are:
- Reviewing of product information targeted at patients
- Contributing to guideline preparation
- Providing advice from a patient perspective in response to specific requests from EMEA Scientific Committees, Working Parties, Scientific Advisory Groups, etc.

People can interpret risks very differently, depending on their situation.

Over the past few years the EMEA has increased its efforts to involve patients in different aspects of drug regulation. The Agency has established the EMEA/CHMP Working Group with Patients’ Organisations, which aims to improve communication with patients, improve the readability of medicines information and enhance the safety of medicines.

The Committee for Orphan Medicinal Products has three members of patients organisations and two members of patients organisations are representatives on the EMEA Management Board.
Chapter 3:
Information about Cancer Drugs
Information about cancer drug approval is available on many regulatory agency websites. In recent years regulators worldwide have made concerted efforts to make information more easily available. The EMEA makes a European Public Assessment Report (EPAR) - a report on the scientific conclusions reached by the CHMP - available on its website for each new marketing authorisation application. The content of the EPAR is derived from the various reports produced during the evaluation procedure and is updated throughout the authorisation period and as conditions of the authorisation (e.g. pharmacovigilance, new indications) are expanded.

In recent years regulators have made concerted efforts to make information more easily available.

The FDA has a special area on its website that provides comprehensive information about different aspects of cancer drug approval. When the FDA makes a decision to approve an important new cancer drug, a press release or talk paper is normally made available that outlines the significance of the approval in an easy-to-read format.

Individual patients need to have clear and comprehensive information about cancer drugs, so that they can take their treatment in a safe and effective manner. Specifically, patients need information about:

- How a drug works
- The clinical benefit of the drug
- The potential risks of taking a drug (i.e. interactions and contra-indications)
- The expected side effects of the drug and how long they will last
- What they can do to prevent and quickly detect drug side effects
- What treatment can help prevent or alleviate side effects

Drugs are normally supplied with a leaflet that contains full information about the drug, which is included in the package (this is called the PIL—see Chapter 2).

While these leaflets provide comprehensive information about the drug, they are often not written in an easy-to-read manner, and patients find them difficult to understand. Moreover, cancer patients who receive their medication in a hospital setting are often not given the PIL that accompanies an injectable medication.

Patients can find information about cancer drugs from a number of other sources. However, some of these sources are unreliable and provide information that is inaccurate, out-of-date or not balanced.

In most countries worldwide pharmaceutical companies are prohibited from providing information directly to patients – notable exceptions are the US and New Zealand. However, some would argue that there are some benefits from companies providing information on their products directly to patients via websites and information booklets. Many US-based pharmaceutical companies have websites that provide information about their products, but these are restricted to US residents.

Individual patients need to have clear and comprehensive information about cancer drugs, so that they can take their treatment in a safe and effective manner.
US-based pharmaceutical companies can also advertise their products to the general public within the US – this is called direct-to-consumer advertising (DTCA). The ethics of whether it is acceptable to allow advertising of pharmaceutical products directly to consumers have been hotly debated. Proponents of DTCA argue that advertisements empower patients by providing them with information they need to make informed choices about treatment, whereas critics counter that it just encourages wasteful prescribing, leads to the medicalisation of diseases (i.e. it fosters the belief that there is a pill for every ill) and is of little value to patients. However, the difference between advertising and information has been overlooked in this polemic debate. It has been argued that there are potential benefits in providing balanced and accurate information about products directly to patients (this is sometimes referred to as direct to consumer information – DTCI). DTCI may be another useful vehicle to help patients take medication safely and adhere to their prescribed treatment regimen – a key consideration given that non-adherence with cancer treatment is an important problem in cancer care today.
Chapter 4:
Access to Cancer Drugs
How can a patient gain access to a drug before it is approved?

Patients who have run out of treatment options can face an agonizing wait for an experimental agent to be approved. However, there are two ways in which a patient with a life-threatening disease can gain access to an unapproved drug – one is via a clinical trial and the other is through some type of compassionate use programme. The simplest way to get access to an unapproved drug is through enrolling in a clinical trial. However, this is not always possible; some patients do not meet eligibility criteria, they may live too far away from a trial centre, or the trial may have closed down or be filled to capacity.

Joining a clinical trial

An important issue is how do patients find out about clinical trials for which they are eligible? For some cancer patients, in whom all licensed treatments have failed, a clinical trial may represent the last hope the patient has of staying alive. Yet, access to trial information is sometimes difficult, if not impossible, to come by.

Traditionally the pharmaceutical company running the clinical trial would reach agreement with one or more physicians that they will be the investigators for a particular trial. For cancer drugs these investigators will usually be specialist oncologists working in well-recognised cancer centres or clinics. It would then be up to the physician to recruit suitable patients as and when he or she encounters them in the clinic. This process arguably has several drawbacks in that it relies on the investigator’s enthusiasm to recruit patients or other physicians’ knowledge that the trial is taking place. Additionally, the advantages of being in a clinical trial are, unfairly, offered only to those patients who happen to attend the recruiting clinic. It also means that the recruitment process is very slow.

Clinical trial registries

Increasingly, in response to public demands for transparency in studies involving humans, pharmaceutical companies and investigating institutions are making information available about clinical trials more widely available; but information is still patchy and variable between countries. A huge number of registers exist worldwide but there is little co-ordination between them and accessibility of information is highly variable. Some registries are slow in updating information and so are out of date or incomplete. In Europe, especially, the registries that do exist do not list phase I trials – and waiting for new drugs to enter phase II or III may be too long to wait for some patients. Currently, one of the most comprehensive registries is clinicaltrials.gov, but the lists are incomplete and cover predominantly trials conducted in the US. Some other trial registries, which cover Europe and other countries, are listed at the end of this document, however the list not comprehensive. Regulatory agencies are also beginning to list trials on their websites.

In 2006, the World Health Organization (WHO) launched the International Clinical Trials Registry Platform (ICTRP), an initiative that has been developed after nearly two years of consultation with all concerned stakeholders, including representatives from the pharmaceutical, biotechnology and device industries, patient and consumer groups, governments, medical journal editors, ethics committees and academics. Although industrial and academic confidential information needs to be protected, the aim of the Registry Platform is to make clinical research transparent, and it includes recommendations that 20 key details be disclosed at the time studies are begun. The Platform will not be a register itself, but will provide a set of standards for all registers. A web-based portal will be launched in late 2006, where scientists, patients, doctors and anyone else who is interested, can search among
participating registers for trial taking place or recently completed throughout the world.

Armed with the knowledge that a trial is taking place, a patient may be able to persuade his or her own doctor to contact the investigating institution. Sometime physicians are reluctant to refer patients to other clinics, this may be because they are convinced that the treatment they prescribe is superior to the trial treatment, or they may not wish to lose control of their patient’s care. If the patient’s own doctor will not help, the patient may contact the trial centre directly. However, it is still the responsibility of the investigating physician to enter a patient into a clinical trial; a patient may volunteer, but cannot demand that they are included in a trial. Patients also have to meet the eligibility criteria (see Chapter 2).

**Compassionate use**

For patients who cannot enrol in a clinical trial, but lack an effective treatment option, compassionate use may offer an alternative. There are a number of ways that patients can gain compassionate access to an unapproved drug. Firstly they can take part in an expanded access programme (EAP) which is similar to a clinical trial in that the patient still has to meet specific requirements such as the type and stage of disease, but the requirements are less stringent than clinical trials. Secondly, if an EAP is not available, patients can gain access to unapproved drugs through a single-patient compassionate use programme (also called a named patient programme). In most countries, patients can import unapproved drugs for their own use as long as the drug has been approved in some other country.

Compassionate use programmes are basically the same across the world, but, as ever, they differ in detail and confusion can arise because of the variety of terms that are used to describe how a patient may get access to an unapproved new drug outside of a clinical trial. In most countries there are laws in place that govern compassionate use programmes and regulatory agencies normally oversee these programmes.

**Table 4: Pre-approval access from selected countries worldwide**

<table>
<thead>
<tr>
<th>Country</th>
<th>Access Options</th>
</tr>
</thead>
</table>
| United States | • Single Patient IND (compassionate use)  
                  • Expanded Access Protocols (EAP)  
                  • Importation of a product approved in another country for personal use |
| United Kingdom | • Open-label clinical trial  
                              • Importation of product approved in another country for personal use  
                              • Supply of drug on a “named patient basis” |
| France     | • Nominatif Autorisation Temporaire d’Utilisation (ATU) – for an individual patient  
                              • Cohort ATU for a group of patients that are treated according to a protocol |
| Germany    | • Named patient sales of products that are approved in another country  
                              • Named patient programme |
| Italy      | • Named patient programme for products approved in another country or that have completed phase II trials  
                              • Importation of a product approved in another country for personal use |
| Canada     | • Special Access Programme that enables patient to access an unapproved drug on the request of a physician and with the agreement of the pharmaceutical company  
                              • Importation of a product approved in another country for personal use |
| Australia  | • Special Access Scheme that allows physicians to prescribe unapproved drugs under certain circumstances  
                              • Importation of a product approved in another country for personal use |
Pharmaceutical companies are not obliged to provide an unapproved drug to patients as part of a compassionate use programme. Some drug companies may refuse compassionate use requests or will not set up a voluntary EAP. There are many reasons for this including:

- Lack of efficacy – there may not yet be good evidence that the drug is effective for the specific illness
- Safety – problems may arise that could compromise approval
- Cost – compassionate use can be expensive, especially large access programmes and the company may not be able to recover the cost through reimbursement
- Production capacity – drugs can be expensive and time-consuming to make, and until approved, capacity to manufacture the drugs may be limited
- Impact on clinical trials – participation in important clinical trials, especially those that are randomised could be affected

Physicians play an important role in helping patients gain access to an unapproved product. Often a physician will have knowledge of an unlicensed drug, usually because he or she is involved in a clinical trial of that drug, and encounters a patient whom he or she feels would stand to benefit from the drug even though they cannot be entered into a clinical trial. It is the physician who must actually get formal approval from the pharmaceutical company and the regulatory agency to use the drug. Often detailed paperwork about the patient must be submitted, including medical history and previous treatments. This can be very time-consuming and certainly requires a huge commitment on the physician's part.

Trying to get an unapproved drug through a compassionate use programme can be frustrating, confusing, time-consuming and often unsuccessful. In an effort to overcome this unsatisfactory experience the EMEA has prepared guidelines to help improve the equity of access of European patients to compassionate use programmes and to encourage EU Member States to follow a common approach regarding the conditions of use and patients targeted in compassionate use programmes. These guidelines relate to EAPs rather than single-patient compassionate use programmes. EMEA intends to establish a public register of CHMP's opinion on the conditions for use of an unapproved drug as part of a compassionate use programme. Implementation of the compassionate use programme will remain the responsibility of the national regulatory agency.

What happens when a drug is approved?

Once a drug is approved a physician is able to prescribe it for the indications for which it has a license, however somebody must pay for the drug. In many countries pharmaceuticals are paid for either fully or partly through public funding – this is known as public reimbursement. However, in some situations, or for some products, patients may have to cover some of the cost themselves through co-payments. These are levied through a fixed fee or a percentage of the cost of the drug. In some countries a limit is imposed on annual expenditure. Where cancer therapies are reimbursed, it is usual for them to be covered 100%, i.e. there is no patient co-payment.

Pricing of pharmaceuticals is often a separate issue and the bodies that determine reimbursement may or may not also agree the price. Pricing and reimbursement procedures can be fast or they can take several years to complete; this can result in considerable delays in patients gaining access to optimal treatment. Some patients gain access to new medicines months, or even years, in advance of others.

A qualified physician is allowed to prescribe a licensed drug for any condition – even for indications not licensed by regulatory agencies. For example the drug may be licensed for use in advanced breast cancer, but based on experience the physician may decide that the drug should be
given to patients with early disease. This is called “off-label” prescribing. Off-label prescribing is not always reimbursed by health authorities, so is often only carried out in private healthcare settings. Off-label prescribing carries additional risk, since clinical studies may not have studied these situations fully.

In an effort to control spending on pharmaceuticals, governments use a vast array of measures to influence the supply and demand for drugs. On the supply side, health authorities can limit the cost of reimbursed medicines by controlling their prices and/or reimbursement. They can also limit the availability of certain drugs though the use of positive and negative lists – drugs on the positive list are reimbursed; those on the negative list are not.

Governments can also control demand for drugs by influencing physician prescribing, and formularies are usually developed that seek to guide the prescribing of reimbursed drugs. Prescribing guidelines and treatment protocols are also used to limit demand for drugs. Some physicians are allocated prescription budgets and asked to consider costs when selecting treatments. Health authorities also encourage physicians to prescribe generic drugs where they exist, and this helps to keep overall healthcare expenditure down while releasing budgets for use on the latest branded therapies.

Increasingly health economic evaluations are being used to guide decisions about whether a drug should be reimbursed and at what price. Health Technology Assessment (HTA) agencies often contribute to this process by providing independent advice on the clinical and/or cost-effectiveness of a particular drug.

For example, the UK’s National Institute of Health and Clinical Excellence (NICE) reviews the clinical and economic evidence about a drug and issues a recommendation as to whether or not the National Health Service (NHS) should invest in and use the drug. One of the reasons behind establishing NICE was to end the inequality that existed in prescribing practices in the UK. Prior to the establishment of NICE, individual healthcare authorities could decide which drugs they would pay for and which ones they would not. The resultant “postcode prescribing” produced many inequalities in the treatment of patients, depending on where they lived. Although the UK NHS is obliged to provide funding within three months of a recommendation being issued by NICE, inequalities still exist. This is partly because NICE is a relatively new body and has not reviewed all the existing medicines on the market, but mainly because it has no power to force local NHS budget holders to use the budgets it has set aside. So, it takes a considerable amount of time to assess new medicines, and even after guidance has been issued, access to new drugs is patchy and the regional variations which NICE intended to eliminate seem as prevalent as ever.

The data used to support the approval of a new drug may not be sufficient to demonstrate the cost-effectiveness of that drug. Such data are sometimes best collected once the drug is in clinical use. This uncertainty around the value of a new medicine can further delay patient access to the product.

Efforts are currently taking place at a European level to promote greater co-operation and sharing of expertise in health technology assessment amongst EU Member States. In particular the development of common information packages has been encouraged to facilitate transferability of assessments between countries. However, it is unlikely that we will see a ‘Euro-NICE’ that would carry out HTAs that would apply to Europe as a whole: differences in clinical practice, product and service acquisition costs, mortality and prevalence of diseases make any pan-European health technology assessment difficult, and comparison of cost-effectiveness impossible.
Chapter 5:
Pharmacovigilance
Monitoring the safety profile of a drug

Despite the thorough testing carried out before a drug is licensed to establish its safety and side-effect profile, a complete picture of safety cannot be obtained until the drug has been in use for some time. Clinical trials are carried out in hundreds or thousands of people, but the population in which the drug is finally used runs to tens of thousands, or even millions. Some serious effects may only occur in 1 in 10,000 patients, making it impossible to detect in a normal development programme. Therefore there are mechanisms in place to track the safety and side effects of drugs: this is pharmacovigilance.

A complete picture of the safety of a drug cannot be obtained until it has been in use for some time.

Adverse event reporting

Regulatory agencies have a system in place for reporting adverse event data and ensuring that the information is available for those that need it. For example, in Europe an electronic tracking and reporting system for safety reports has been introduced (www.eudravigilance.org), with the aim of establishing a reporting system based on standardised pharmacological data.
Regulatory agencies have systems in place for reporting adverse event data and ensuring that the information is available for those that need it.

Product recalls

Pharmaceutical products may be recalled by the manufacturer or a regulatory agency. A recall can mean that just a particular batch or all of a certain product is returned to the manufacturer, because the safety, quality, or efficacy of a distributed product may be compromised.

Products may be recalled for a variety of reasons; some are not medically significant but others can be potentially very serious.

Recalls can be triggered for a variety of reasons. Some are not medically significant – for example, the packaging could be wrong. But others can be very serious; possibly a patient has had a serious adverse reaction; the formulation of the product may be incorrect; or the product stability is not acceptable.
Further Reading


Regulatory Agency Websites

European Medicines Agency (EMEA)
http://www.emea.eu.int/

US Food and Drug Administration (FDA)
http://www.fda.gov/

Health Canada
http://www.hc-sc.gc.ca

Australian TGA
http://www.tga.gov.au

Austria: Bundesministerium für Gesundheit und Frauen
www.bmsg.gv.at

Belgium: Directoraat generaal Geneesmiddelen/Direction générale Médicaments
www.afigp.fgov.be

Cyprus: Ministry of Health
www.pio.gov.cy

Czech Republic State Institute for Drug Control
www.sukl.cz

Denmark: Lægemiddelstyrelsen
www.dkma.dk

Estonia: State Agency of Medicines
www.sam.ee

Finland: Lääkelaitos
www.nam.fi

France: Agence Française de Sécurité Sanitaire des Produits de Santé
www.afssaps.sante.fr

Germany: Bundesinstitut für Arzneimittel und Medizinprodukte
www.bfarm.de/de/index.php

Greece: National Organisation for Medicines
www.eof.gr

Hungary: National Institute of Pharmacy
www.ogyi.hu

Ireland: Irish Medicines Board
www.imb.ie

Italy: Ministero della Salute
www.ministerosalute.it

Japanese agency

Latvia: Food and Veterinary Service
www.zaale.vza.gov.lv

Lithuania: State Medicines Control Agency
www.vvklt.lt

Luxembourg: Ministère de la Santé Division de la Pharmacie et des Médicaments
www.etat.lu/MS

Malta: Medicines Authority
www.medicinesauthority.gov.mt/

Netherlands: Staatstoezicht op de volksgezondheid, Inspectie voor de Gezondheidszorg
www.igz.nl

College ter Beoordeling van Geneesmiddelen (CBG)
http://www.cbg-meb.nl

Norway: Statens Legemiddelverk
www.legemiddelverket.no

Poland: Office for Medicinal Products
http://www.urpl.gov.pl

Portugal: Instituto Nacional da Farmácia e do Medicamento
www.infarmed.pt

Slovak Republic: State Institute for Drug Control
www.sukl.sk

Slovenia: Agency of the Republic of Slovenia for Medicinal Products and Medical Devices
http://www2.gov.si/mz/mz-splet.nsf

Spain: Agencia española del medicamento
www.agemed.es

Sweden: Läkemedelsverket
www.mpa.se

Switzerland: Swissmedic
http://www.swissmedic.ch/

United Kingdom: Medicines and Healthcare products Regulatory Agency
www.mhra.gov.uk
Other Websites Related to Drug Regulation

ICH

WHO Medicines Policy and Standards

EU Commission: DG Enterprise and Industry (pharmaceuticals)
http://ec.europa.eu/enterprise/pharmaceuticals/index_en.htm

Orphanet (Rare diseases and orphan drugs)
www.orpha.net

Declaration of Helsinki
http://www.wma.net/e/policy/b3/htm

Nuremberg Code
http://osher.od.nih.gov/guidelines/nuremberg.html

Health Technology Assessment Agency Websites

Germany: Institute for Quality and Economic Evaluation in Healthcare (Institut fuer Qualitaet und Wirtschaftlichkeit im Gesundheitswesen or IQWiG)
www.iqwig.de

UK: National Institute of Clinical Excellence (NICE)
www.nice.org.uk

Clinical Trial Registry Websites

US (and some ex-US)
www.clinicaltrials.gov

Australia
www.actr.org.au

Controlled Trials
www.controlled-trials.com

Meta Register of controlled trials
www.controlled-trials.com/mrct

National Cancer Research Institute
www.cancertrials.org.uk

International Federation of Pharmaceutical Manufacturers and Associations
http://clinicaltrials-dev.ifpma.org/

Cancer Research UK Find a Clinical Trial
http://www.cancerhelp.org.uk/trials/trials/default.asp

Cancer Index Clinical Trials
http://www.cancerindex.org/clinks4t.htm

CentreWatch Clinical Trial Listing Service
http://www.centerwatch.com/

The WHO International Clinical Trials Registry Platform
www.who.int/ztcrp/

Emerging Medicines
www.emergingmed.com/
(Note there is also a website www.emergingmeds.com - with an "s". This is not a useful site for cancer clinical trials)
## Abbreviations

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<th>Abbreviation</th>
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<td>AFSSPS</td>
<td>Agence Française de Sécurité Sanitaire des Produits de Santé (The French Regulatory Agency)</td>
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<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use</td>
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<td>CR</td>
<td>Complete response</td>
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<td>CT</td>
<td>Computerised Tomography</td>
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<td>DFS</td>
<td>Disease free survival</td>
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<td>DSMB</td>
<td>Data and Safety Monitoring Board</td>
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<td>DTCA</td>
<td>Direct to consumer advertising</td>
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<td>DTCI</td>
<td>Direct to consumer information</td>
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<td>EAP</td>
<td>Expanded Access Programme</td>
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<td>EEA</td>
<td>European Economic Area</td>
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<td>EFTA</td>
<td>European Free Trade Area</td>
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<td>EMEA</td>
<td>European Medicines Agency</td>
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<td>EPAR</td>
<td>European Public Assessment Report</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<td>HTA</td>
<td>Health Technology Assessment</td>
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<td>ICH</td>
<td>International Conference in Harmonisation of Technical Requirements for Registration of Pharmaceuticals</td>
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<tr>
<td>ICTRIP</td>
<td>International Clinical Trials Registry Platform</td>
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<tr>
<td>INN</td>
<td>International non-proprietary name</td>
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<tr>
<td>MHRA</td>
<td>Medicines and Healthcare products Regulatory Agency</td>
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<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
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<tr>
<td>NICE</td>
<td>National Institute for Clinical Excellence</td>
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<td>ODAC</td>
<td>Oncology Drug Advisory Committee</td>
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<td>PFS</td>
<td>Progression free survival</td>
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<td>PIL</td>
<td>Patient Information Leaflet</td>
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<td>PPI</td>
<td>Proposed Package Insert</td>
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<td>PR</td>
<td>Partial response</td>
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<td>QOL</td>
<td>Quality of Life</td>
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<td>RECIST</td>
<td>Response Evaluation Criteria in Solid Tumours</td>
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<td>SmPC</td>
<td>Summary of medicinal Product Characteristics</td>
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<td>WHO</td>
<td>World Health Organisation</td>
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Glossary of Terms

active control trial: A type of clinical trial in which the new drug is compared with a standard treatment so both arms of the trial receive active medication and no one receives placebo.

adjuvant therapy: Therapy given in addition and as a supportive therapy to another kind of therapy. Usually chemotherapy is given as an adjuvant to surgery or radiotherapy.

advanced cancer: Cancer diagnosed at a late stage when it has spread (metastasised) to other areas of the body.

apoptosis: A mechanism of programmed cell death. It is a natural part of the functioning of the body – a way to remove unwanted or worn out cells. However, cancer cells can evade this pathway so even if they are unwanted or should be “worn out” they continue to live and grow.

angiogenesis: The process of the formation of new blood vessels. As tumours grow they need new blood vessels to populate the tumour and supply oxygen and nutrients to the growing cell mass.

arm: Any of the treatment groups in a randomized trial. Most randomized trials have two “arms,” but some have three “arms,” or even more.

best supportive care: The standard of care that is accepted to be the best that can be provided without active treatment of the disease.

biomarkers: A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention. This term is used in two contexts: firstly the tumour response to treatment may be assessed by response biomarkers, that is a biochemical parameter that is an indicator of tumour shrinkage or growth. Biomarkers are also the biochemical markers that help reveal the nature of the biological changes in the cell that has produced the cancer. If a suitable predictive biomarker can be identified it will allow us to select the patients who will respond to a particular targeted therapy.

carcinoma: Cancer arising from epithelial tissue. Epithelium includes the skin and the tissue that covers or lines the internal organs.

cell line: Animals cells grown in the laboratory in dishes. The cells have been investigated and documented so that their characteristics are well known and they can be used for screening or research purposes.

clinical trials: A clinical trial is a research study to answer specific questions about vaccines or new therapies or new ways of using known treatments. Clinical trials (also called medical research and research studies) are used to determine whether new drugs or treatments are both safe and effective. Carefully conducted clinical trials are the fastest and safest way to find treatments that work in people. Trials are in four phases: Phase I tests a new drug or treatment in a small group; Phase II expands the study to a larger group of people; Phase III expands the study to an even larger group of people; and Phase IV takes place after the drug or treatment has been licensed and marketed.

cohort: In epidemiology, a group of individuals with some characteristics in common.

compassionate use: The provision of drugs by a pharmaceutical company before it has been granted marketing authorisation to patients who are unable to enter a clinical trial. Theses supplies are made on compassionate grounds.

complete response: A complete response denotes that all visible tumour has been eradicated by the treatment.

contraindications: Any factor in a patient’s condition that would make it unwise to pursue a particular line of treatment.

control: The control is the comparator of an active drug. The control group or control arm may receive standard therapy with which the new therapy is being compared or may receive a placebo.
**controlled trial:** The term for a clinical trial that possesses a control arm.

**crossover:** When patients fail treatment in one arm of a trial they can be “crossed-over” to another arm to see if a response can be achieved.

**cytostatic:** A drug that prevents cells growing further or replicating.

**Data and Safety Monitoring Board:** An independent committee that has the responsibility of ensuring that the risks of participation in a clinical trial are and continue to be acceptable.

**dilution effect:** An effect on the results of a trial that make a drug appear less effective. This happens because the drug is being examined in a broad mixed population, when it has different levels of efficacy against different groups within the population. If only the true responders were included the drug would appear more efficient; when non-responders are include the results are diluted.

**direct to consumer advertising:** The advertising of medicines by the manufacturer to patients.

**direct to consumer information:** The provision of information about medicines from the manufacturer directly to patients.

**disease free survival:** The length of time following treatment that a patient survives without any evidence of detectable disease.

**disease progression:** The condition when a tumour continues to grow and increase in size.

**dose-limiting toxicity:** Side effects that are severe enough to prevent giving more of the treatment. New drugs are tested in phase I clinical trials by giving cohorts of patients increasing doses of drug. The first cohort typically gets a very low dose, and the dose is raised in each subsequent cohort until a set number of patients experience the dose limiting toxicity. The dose level used for the previous cohort to this last cohort is then taken to be the maximum tolerated dose.

**double-blind trial:** The term for a clinical trial in which neither the investigating physician and staff nor the patients have knowledge of which arm of the trial the patient is in.

**drug label:** This term is used rather broadly and can mean different things depending on the context. The EU definition is the information on the immediate or outer packaging. In the US labelling is considered to be all the documentation that the manufacturer has submitted to the FDA for a medicinal product. The very wide definition of labelling gives the FDA more control over the promotional practices of pharmaceutical companies. The term “off label” refers to use of the drug for an indication for which it does not have a licence.

**dysfunction:** Abnormal function.

**early cancer:** Cancer diagnosed when it is small and discrete and stands a good chance of being curable.

**eligibility criteria:** The list of criteria that define participant selection for a clinical trial; it includes inclusion and exclusion criteria.

**endocrine therapy:** Treatment that involves hormones or more often preventing the action of hormones.

**endpoint:** What a clinical trial is trying to measure or find out. In essence, the goal of the trial. It is scientifically very important that the goals for clinical trials be selected and clearly defined in advance. Typical end points include measurements of toxicity, response rate, and survival.

**enzymes:** Proteins in cells that facilitate biochemical reactions crucial to cell functioning.

**evaluable disease:** A tumour or tumours which you can tell are present but the size of which cannot be measured accurately. For example, for technical reasons, bone metastases are hard to measure exactly and are usually counted as evaluable disease. The same is true for pleural effusions (fluid around the lungs), and ascites (fluid in the abdomen).
**Glossary of Terms**

**excipient:** A substance that is combined with a drug in order to render it suitable for administration. Excipients should have no pharmacological activity themselves.

**exclusion criteria:** The criteria that define which people cannot be included in a clinical trial.

**expanded access programme:** Drugs may be supplied to patients before they have marketing authorisation on compassionate grounds. This may be formalised into an expanded access programme when patients are monitored and data are collected in a similar manner to a clinical trial.

**Good Clinical Practice:** An international ethical and scientific quality standard for designing, recording and reporting trials that involve the participation of human subjects. Compliance with this standard ensures that the rights, safety and well-being of trial subjects are protected.

**half-life:** The time it takes for half the dose of drug to be eliminated from the body. So if 10 units of a drug with a half life of one day is given, after 1 day there will be 5 units in the blood, after 2 days 2.5 units, after 3 days 1.25 units and so on until the drug is eliminated.

**health technology assessment:** An appraisal of a drug’s efficacy in relation to its costs, what costs is saves and in comparison to other medicines for the same condition.

**inclusion criteria:** The criteria that define which people should be included in the clinical trial.

**indication:** The disease and patient group for whom the drug has a marketing authority or licence.

**informed consent:** The agreement a patient gives to enter a clinical trial. It is important that the patient has received a full explanation of what the trial involved and why it is being conducted and that their consent is voluntary.

**International Clinical Trials Registry Platform:** A WHO initiative to provide a portal where clinical trial registries can be accessed by the public.

**leukaemia(s):** A group of malignant diseases in which the bone marrow or other blood-forming organs produce increased numbers of certain types of white blood cells.

**lymph nodes:** The lymphatic system is a network of vessels that conveys electrolytes, water, proteins etc. in the form of lymph. Lymph nodes are small swellings comprised of lymphoid tissue which act as filters for the lymph and prevent foreign particles from entering the bloodstream. Cancer cells can spread via the lymphatic system and may get trapped in lymph nodes.

**lymphocyte:** Types of white blood cells that form an important part of the immune system.

**lymphoid:** Tissue that produces white blood cells (lymphocytes) and antibodies. It occurs as discrete organs, the lymph nodes, tonsils, thymus and spleen and also as diffuse groups of cells.

**lymphoma:** Any tumour of the lymphatic system. There is a group of several different lymphomas.

**maximum tolerated dose:** In order to increase drug activity it will usually be given at the highest dose that does not cause unacceptable side effects. This is the maximal tolerated dose.

**measurable disease:** Disease that can be visualised by some imaging technique and measured objectively.

**metastases:** “Secondary tumours” that have formed from spread of cells from the primary tumour.

**metastasis:** The process whereby individual cell detach from a tumour and travel to another part of the body where they start to grow as secondary tumours or metastases. Cells travel by three main routes: the blood the lymphatic system or across body cavities. Metastatic adj. Metastasise vb.

**metastasising:** The process of a cancer spreading in the body.

**molecular pathways:** The pathways inside cells that control their function.
**monoclonal antibodies**: Antibodies that have been produced in the laboratory. They are called monoclonal as they consist of a population of antibodies that are all exactly the same. These antibodies are used for experimental and therapeutic purposes.

**multicentre trial**: A trial that is carried out at more than one location. The trial centres may be in one country or in several different countries.

**multiple myeloma**: Multiple myeloma (also known as myeloma or plasma cell myeloma) is a progressive haematologic (blood) disease. It is a cancer of the plasma cell, an important part of the immune system that produces antibodies. Multiple myeloma is characterized by excessive numbers of abnormal plasma cells in the bone marrow and overproduction of antibodies.

**National Institute of Clinical Excellence**: NICE is a UK independent organisation responsible for providing national guidance on promoting good health and preventing and treating ill health. NICE provides guidance on the use of new and existing medicines, treatments and procedures within the NHS. Drugs given a positive NICE approval must be supplied by the NHS in the UK.

**neo-adjuvant therapy**: Therapy, usually chemotherapy, given to shrink a tumour so that it is possible to then remove it surgically.

**neutropenia**: A low number of white blood cells. As these are the cells involved in fighting infection, neutropenia renders people susceptible to infection by bacteria, viruses, fungi etc.

**non-comparator studies**: Clinical trials in which a drug is not compared with any other drug.

**non-inferiority trial**: A non-inferiority trial is where the new drug is a compared to the standard with the aim being to show better tolerability and possibly quality of life for the new drug but no important difference in survival time.

**open-label trials**: Trials in which the doctor and patients know who is receiving which drugs.

**orphan drugs**: Drugs that are designed to treat very rare diseases.

**optimal biological dose**: Biological therapies do not behave in the same way as conventional drugs, so instead of using the maximal tolerated dose*, these agents are given at the dose that give the most beneficial biological activity.

**overall survival**: The length of time a group of patients survive after completing a clinical trial.

**overexpression**: Over production of a component in the cell. This occurs because the gene is transcribed more than usual and more gene products are produced or because the number of copies of the gene is increased.

**partial response**: Roughly speaking, a decrease in the amount of cancer of at least 50%, but less than 100%. More precisely, a decrease in the total cross sectional area of all measurable tumours of at least 50% but less than 100%.

**patient information leaflet**: A leaflet providing comprehensive information on a drug that has to be approved by regulatory authorities when the drug gains a licence and is included within the drug packaging.

**patient reported outcome**: A report made by the patient about how they feel or have responded to a medication. Patient reported outcomes are useful but may be subject to variability between individuals as opposed to physician reported outcome as the physician should report on each patient using the same judgement.
Glossary of Terms

**pharmacodynamic studies**: The interaction of drugs with cells. It includes such factors as their uptake and intracellular metabolism.

**pharmacokinetic studies**: The handling of a drug within the body, which includes its absorption, distribution, metabolism and excretion.

**pharmacovigilance**: Also called “post-marketing surveillance” is the continual monitoring of licensed drugs for safety and efficacy.

**Phase 1**: A Phase 1 clinical trial is the first step in testing a new investigational medication (or new use of a marketed drug) in humans.

**Phase 2**: Phase 2 clinical trials involve volunteers who have the disease or condition to be treated. These trials help physicians and researchers begin to learn more about the safety of the new drug treatment and how well the drug treats the targeted disease or condition.

**Phase 3**: A Phase 3 trial usually compares how well the study drug works compared with an inactive placebo and/or another approved medication.

**Phase 4**: Phase 4 studies are carried out once a drug has received marketing authorisation. They may be carried out to determine whether the drug is effective against other disease states, to test different ways of taking the drug such as time-release capsules or syrups, or to look for adverse events in larger populations over longer periods of time.

**placebo**: An inert “dummy” pill or injection that matches the active drug in appearance. A placebo is given to one arm of a trial to allow the active drug to be compared with the effect of taking no active medication.

**placebo-controlled**: A clinical trial in which the active drug is compared with a placebo.

**placebo effect**: The effects on a patient of taking a placebo. People will often produce real clinical responses to a placebo, even though it does not contain active medication, for psychological reasons (e.g. they are responding to increased attention from healthcare professionals).

**predictive biomarker**: A biomarker that gives some indication of whether an individual is likely to respond to particular treatment. For example anti-HER 2 antibodies are only given to women whose breast tumour contains the HER 2 receptor.

**prevalence**: The number of people with a certain disease in a population. It is usually expressed as the number of people with conditions per 1,000 of the population.

**primary endpoint**: The main parameter that the trial has been designed to evaluate.

**progression free survival**: The time a patient lives without any worsening of the disease.

**proposed package insert**: The US document that summarises all the known information about the drug including which patients can receive the drug and for which indication: how often the drug should be taken; what are the contra-indications and side effects and what monitoring is required.

**protocol**: The precise details of the way a clinical trial is to be carried out.

**quality of life**: A measure of how people are able to function in everyday living and how satisfied they are with their own perception of their everyday living.

**radio resistant**: Not susceptible to destruction by radiation in the normal doses used.

**randomisation**: The distribution of patients randomly into different arms of a clinical trial. Randomisation is carried out using computer programs.

**receptors**: Specialised parts of cells that are stimulated by molecules (called ligands) and will then pass messages onto other parts of the cell. Many receptors are on the cell’s surface others are in the cell nucleus. Many receptors respond to growth factors that cause the cell to grow and divide.

**refractory disease**: Disease that is not responding to treatment.
regimen: A prescribed systematic form of treatment, such as a medication, diet, or exercises, for curing disease or improving health.

reimbursement: The act of compensating someone for an expense. Health authorities will cover the costs of certain medications and medical devices. The process whereby the health authority pays the healthcare provider (e.g. hospital or pharmacists) who has delivered the medication or device is called reimbursement.

resistant: A condition where a disease ceases to respond to a previously effective treatment.

response biomarkers: See biomarkers.

response rate: (In cancer trials) A measure of whether the tumour shrinks in size during treatment.

sarcoma: A cancer arising in muscle or connective tissue.

salvage therapy: The name given to the chemotherapy regimen employed when another treatment has failed. It may also be called second line, third line therapy etc.

secondary endpoint: Secondary parameters that will be evaluated in the trial. These are determined alongside the primary endpoint.

single-blind trial: A trial in which the investigators knows which patient is in which arm of the trial.

sponsor: The company or institution paying for the clinical trial.

stable disease: The situation where there is no measurable disease progression.

stage: The stage of a cancer defines how advanced the disease is and whether it has spread from its initial location. To stage (vb) a patient means to determine the presence and site of metastases in order to plan treatment.

stratification: Dividing a cohort of patients into groups with similar properties in terms of age, gender, previous medical history etc.

summary of medicinal product characteristics: The European document that summarises all the known information about the drug including which patients can receive the drug and for which indication: how often the drug should be taken; what are the contra-indications and side effects and what monitoring is required.

superiority trial: A clinical trial where a new drug is compared to standard treatment to show superior benefit of the new treatment (e.g. a longer time free from worsening (progression) of the cancer or a longer survival time).

surrogate endpoint: A laboratory finding (results of blood tests for example) or physical signs in a patient (for example shrinkage of a tumour) which are not direct measurements of how a patient feels, functions or survives, but is reasonably likely to predict clinical benefit.

symptom control: Reduction or containment of the symptoms caused by the cancer.

systemically: An effect that occurs throughout the whole body or system. Agents given into the blood act systemically.

teratogenicity tests: Tests designed to investigate any potential for a drug to cause birth defects in the young when taken by a pregnant animal or woman.

time to progression (TPP): The time it takes from a trial's initiation for a patient's tumour to progress.

toxicity: The degree to which a substance is poisonous or produce untoward effects. Toxicity is also described by the terms side effects or adverse events.

toxicological tests: The tests designed to examine and side effects or potentially “poisonous” aspects of a drug.
EMEA is a decentralised body of the European Union with headquarters in London. Its main responsibility is the protection and promotion of public and animal health through the evaluation and supervision of medicines for human and veterinary use throughout the European Union.

The European system for authorising medicinal products was introduced in 1995 providing a centralised and a mutual recognition procedure. It is primarily involved in the centralised procedure, where companies submit one single marketing authorisation application to the EMEA. A single evaluation is carried out by the Committee for Medicinal Products for Human Use (CHMP). On the basis of this evaluation the CHMP will make a recommendation as to the approvability of the product (this is called an opinion). The CHMP opinion is sent to the European Commission so that a decision can be made on whether a single marketing authorisation, valid for the whole European Union, can be awarded.

The mutual recognition or decentralised procedure is where a marketing authorisation granted by the Reference Member State (country which first approves a product in the EU) is recognised by other Member States.

The Committee for Medicinal Products for Human Use (CHMP)

The CHMP is responsible for preparing the Agency’s opinions on all questions concerning medicinal products for human use.

In the ‘Community’ or ‘centralised’ procedure, the CHMP is responsible for conducting the initial assessment of medicinal products for which a Community-wide marketing authorisation is sought. The CHMP is also responsible for several post-authorisation and maintenance activities, including the assessment of any modifications or extensions (‘variations’) to the existing marketing authorisation.

In the ‘mutual-recognition’ and ‘decentralised’ procedures, the CHMP arbitrates in cases where there is a disagreement between Member States concerning the marketing authorisation of a particular medicinal product (‘arbitration procedure’). The CHMP also acts in referral cases, initiated when there are concerns relating to the protection of public health or where other Community interests are at stake (‘Community referral procedure’).

The CHMP is composed of:
- a chairman, elected by serving CHMP members;
- one member (and an alternate) nominated by each of the 25 EU Member States;
- one member (and an alternate) nominated by each of the EEA-EFTA states Iceland and Norway;
- up to five co-opted members, chosen among experts nominated by Member States or the EMEA and recruited, when necessary, to gain additional expertise in a particular scientific area.

Members serve for a renewable period of three years.

European Drug Approval System

Assessments conducted by the CHMP are based on purely scientific criteria and determine whether or not the products concerned meet the necessary quality, safety and efficacy requirements (in accordance with EU legislation, particularly Directive 2001/83/EC). These processes ensure that medicinal products have a positive risk-benefit balance in favour of patients/users of these
products so may be licensed or given marketing authorisation.

The use of the centralised procedure is compulsory for cancer drugs, medicinal products derived from biotechnology and optional for new chemical entities that are deemed to constitute a significant innovation. Under the centralised procedure the granting of authorisation allows the applicant to market the product throughout the EU. The centralised procedure follows a strict timetable that includes the following phases:

**Opinion phase**

The CHMP appoints two of its members to act as rapporteur and co-rapporteur for the coordination of a scientific evaluation of an application. Having considered this evaluation the committee then has to provide an opinion as to whether or not the product should be authorized. Where appropriate, the CHMP may ask the applicant to provide additional information (clock stops). The maximum timeframe for the opinion phase is 210 days excluding clock stops when companies have to provide additional information about the product.

Upon receipt of the CHMP’s opinion the Commission services have 15 days to check that the marketing authorisation complies with Community law and to prepare a draft decision that is then forwarded to the Member States and the applicant.

The Member States have 22 days in which they are allowed to raise objections about the draft decision. If a Member State identifies important new questions of scientific or technical nature the Commission can refer the application back to the Agency for further consideration or convene a plenary meeting of the Standing Committee on Medicinal Products for Humans.

If no significant issues are raised by the Member States the draft decision is submitted to the Standing Committee on Medicinal Products for Humans and this committee delivers its opinion on the draft. If the Committee gives a favourable opinion, the draft decision is adopted by the Commission and notification of marketing authorisation will be sent to the Member States and the marketing authorisation holder in their respective languages. The decision is then published in the Official Journal of the European Communities.

**Decision making phase**

The CHMP opinion is then translated into the official Community languages and sent to the applicant, the Commission and the 25 Member States (plus Norway, Lichtenstein and Iceland). At this stage, the applicant has the right of appeal to the Agency before a final decision on the application is adopted by the Commission. In the case of an unfavourable opinion the company has the right to appeal. It takes some days to translate the CHMP opinion into the various EU languages.
European Public Assessment Report

The CHMP publishes a European Public Assessment Report (EPAR) for every centrally authorised product that is granted a marketing authorisation, setting out the scientific grounds for the Committee’s opinion in favour of granting the authorisation, plus a ‘summary of product characteristics’ (SmPC), labelling and packaging requirements for the product, and details of the procedural steps taken during the assessment process. EPARs are published on the EMEA’s website, and are generally available in all official languages of the EU.

Scientific Assessment Work

Scientific assessment work conducted by the CHMP is subject to an internal peer-review system to safeguard the accuracy and validity of opinions reached by the Committee. The EMEA peer review evaluation system works through a network of European experts made available to the Agency by the national competent authorities of the 25 European Union Member States and the 3 EEA-EFTA States Iceland, Liechtenstein and Norway. These experts serve either as members of the EMEA scientific committees, of the working parties or as part of the scientific assessment teams.
Scientific Advisory Committees (SAGs)

Scientific Advisory Committees are created by the CHMP to provide answers, on a consultative basis, to questions posed by the CHMP. There are several different SAGs which are comprised of experts in the relevant field. So the SAG for cancer drugs is the SAG-Oncology or SAG-O.

The SAG-O consists of core members, who ensure consistency, plus other individual experts who are consulted for their particular expertise as required, on a case-by-case basis. Members of SAG-O are independent experts and provide expertise in clinical trial methodology, as well as the relevant areas of science and medicine. The list of SAG members is available to the public.

SAGs report back to the CHMP, and it is the responsibility of the CHMP to take a decision on any drug marketing authorisation application.

A network of some 3,500 European experts is available for consultation to underpin the scientific work of EMEA.

The CHMP works with the pharmaceutical industry and provides assistance and advice about drug development and clinical trials. It also provides scientific and regulatory guidelines for the industry.

CHMP Working Parties

The CHMP establishes a number of working parties at the beginning of each three-year mandate. These working parties have expertise in a particular scientific field, and are composed of members selected from the European experts list maintained by the EMEA. The CHMP consults its working parties on scientific issues relating to their particular field of expertise, and delegates certain tasks to them associated with the scientific evaluation of marketing authorisation applications or drafting and revision of scientific guidance documents.

Accelerated Assessment

Accelerated assessment is a mechanism for speeding the approval of drugs that meet the following three cumulative criteria:

- Indicated for the treatment of heavily disabling or life-threatening disease
- Absence of an appropriate alternative therapeutic approach
- Anticipation of exceptionally high therapeutic benefit.

If the company considers that the medicinal product meets all these criteria, it can submit a request for accelerated evaluation with an appropriate justification. Upon receipt of a request for accelerated assessment, the Rapporteur/Co-Rapporteur will report to the CHMP, which will take a decision at their next meeting. When deciding on the validity of an application for accelerated assessment, the CHMP will take into account the views of its members as well as the arguments put forward by the applicant. The CHMP should then give an opinion by day 150 following the application (the maximum time for usual applications is 210 days)


Conditional Approval

If there is a pressing need for a drug it may be given conditional approval. There are processes that allow approval to be granted on the basis of phase II studies in certain, well defined, situations. Approval in this context is based on evidence of the drug's activity on surrogate endpoints. A fundamental component of this process is that the company must continue testing after approval in order to demonstrate that the drug provides therapeutic benefit to the patient. So in effect the approval is coming earlier on in the process of collecting the full dossier of information on the drug, but the sponsor is still collecting evidence to complete the drug's dossier, even though this occurs after approval.
Conditional marketing approval is valid for only one year and then will need to be reviewed again by the CHMP. The authorisation is renewable and once pending studies have been completed and accepted it can become a “normal” marketing authorisation.

Approval of Drugs in Exceptional Circumstances

In exceptional cases drugs can be given a marketing authorisation in the absence of a full dossier of information.

Products for which the applicant can demonstrate in this application that he is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because:

• the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, or
• in the present state of scientific knowledge, comprehensive information cannot be provided, or
• it would be contrary to generally accepted principles of medical ethics to collect such information,

may be eligible for marketing authorisation under exceptional circumstances.

Pharmacovigilance

Subsequent monitoring of the safety of authorised products is conducted through the EU’s network of national medicines agencies, in close cooperation with healthcare professionals and the pharmaceutical companies themselves. The CHMP plays an important role in this EU-wide pharmacovigilance activity by closely monitoring reports of potential safety concerns (adverse drug reaction reports, or ADRs) and, when necessary, making recommendations to the European Commission regarding changes to a product’s marketing authorisation or the product’s suspension/withdrawal from the market.

In cases where there is an urgent requirement to modify the authorisation of a medicinal product due to safety concerns, the CHMP can issue an ‘urgent safety restriction’ (USR) to inform healthcare professionals about changes as to how or in what circumstances the medication may be used.
The FDA’s mission is:

- To promote and protect the public health by helping safe and effective products reach the market in a timely way,
- To monitor products for continued safety after they are in use, and
- To help the public obtain the accurate, science-based information they need to improve health.

The assessment, management and communication of the risks associated with drugs that have a marketing authority is the responsibility of the Centre for Drug Evaluation and Research (CDER). CDER has a staff of about 1800, half of which are physicians or scientists. Therefore, around 90% of its scientific work is carried out in-house, by contrast with the EU system. However, the CDER is still free to consult outside expertise if it wishes to do so.

Investigational New Drug (IND) Application

An IND application is the submission of early scientific data about a new drug that allows it to proceed with a clinical trial. An IND application includes preclinical pharmacological and toxicological data, drug manufacturing information and the clinical trial protocols including information on the scientists and physicians who will be involved in the clinical trials. The approval of an IND application is the start of a close collaboration between the CDER and the sponsoring company which leads to the new drug application (NDA).

Federal Law requires that drugs have an approved marketing application before they are transported or distributed across State lines. The IND is a way of releasing pre-approval drugs from that legal requirement so that the drug can be distributed for use in clinical trials.

New Drug Application (NDA)

The actual submission for marketing approval is the New Drug Application. Since the IND has already been submitted the CDER will already have received a lot of information about the new drug, so normally only evidence of efficacy and safety have to be provided at this stage. The application will be considered by the CDER and advice and opinion is sought from a disease-specific advisory committee.

The Oncology Drug Advisory Committee (ODAC)

The committee that assesses cancer drugs is ODAC, this committee meets regularly and the FDA has recently made an agreement with the US National Cancer Institute to share knowledge and resources in order to facilitate the development of cancer drugs and speed their delivery to patients. The committee’s recommendations are not binding on CDER, but the agency will take them into account. CDER can request additional information or revisions. It also inspects manufacturing sites and clinical trial sites and licenses the former. A calendar of ODAC meetings, minutes of previous meetings and information about ODAC members is available on the FDA website in an area called “Oncology Tools”. Not every cancer drug application will go via the ODAC.

Final Approval

Once a decision to approve or not approve a drug has been reached, the decision is evaluated by the director of the applicable drug review division, who makes the final FDA ruling. Once the director has signed an approval action letter, the product can be legally marketed in the United States.
Accelerated Approval

Accelerated approval is a highly specialised mechanism for speeding development of drugs that promise significant benefit over existing therapy for serious or life-threatening illnesses for which no therapy exists. Accelerated development/review can be used under two special circumstances: when approval is based on evidence of the product’s effect on a “surrogate endpoint,” and when the FDA determines that safe use of a product depends on restricting its distribution or use. A surrogate endpoint is a laboratory finding or physical sign that may not be a direct measurement of how a patient feels, functions, or survives, but is still considered likely to predict therapeutic benefit for the patient. The fundamental element of this process is that the manufacturers must continue testing after approval to demonstrate that the drug indeed provides therapeutic benefit to the patient. If not, the FDA can withdraw the product from the market more easily than usual.
**Priority Drug Review**

Another mechanism that the FDA uses to speed up approval of new drugs is the priority drug review process. Drugs deemed to have the greatest potential for medical benefit are given priority treatment and reviewed within six months. The review process is essentially the same as the standard procedure.

**Treatment Investigational New Drugs (Treatment IND)**

Treatment INDs are used to make promising new drugs available to desperately ill patients as early in the drug development process as possible. The FDA permits an investigational drug to be used under a treatment IND, while the clinical trials are still in progress, if there is preliminary evidence of drug efficacy and the drug is intended to treat a serious or life-threatening disease, or if there is no comparable alternative drug or therapy available to treat that stage of the disease in the intended patient population. Additionally, patients treated under Treatment INDs are not eligible to be in the definitive clinical trials, which must be well underway, if not almost finished.

An immediately life-threatening disease means a stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment. For example, advanced cases of AIDS, herpes simplex encephalitis, and subarachnoid haemorrhage are all considered to be immediately life-threatening diseases. Treatment INDs are made available to patients before general marketing begins, typically during Phase 3 studies. Treatment INDs also allow FDA to obtain additional data on the drug’s safety and effectiveness.

**Fast Track process**

FDA's fast track programmes are designed to facilitate the development and expedite the review of new drugs that are intended to treat serious or life threatening conditions and that demonstrate the potential to address unmet medical needs (fast track products). The fast track classification thus does not apply to a product alone, but applies to a combination of the product and specific indication for which it is being studied. The indication, for the purposes of this document, includes both the condition for which the drug is intended (e.g., lung cancer) and the anticipated or established benefits of use (e.g., increased survival). The fast track process therefore refers to the actual development programme for a specific drug for a specific indication that will receive fast track designation. The benefits of this process include scheduled meetings to seek FDA input into clinical development plans and to reach early agreement on the design of the major clinical efficacy studies that will be needed to support approval. The company also has the option of submitting the marketing authorization application in sections rather than all components simultaneously, and the option of requesting evaluation of studies using surrogate endpoints (see accelerated approval). The fast track designation does not necessarily lead to priority review or accelerated approval.

**Pharmacovigilance**

It is mandatory that all adverse events that occur during a clinical trial are reported to the FDA. All other reporting of adverse events is voluntary.

The FDA has a programme called MedWatch that encourages on-line reporting of all drug adverse events, errors in drug use and product quality problems. This site provides mechanisms for physicians to report adverse events, but also encourages individuals to report any adverse events. It is preferable that the individual takes the report form to their local physician to get the medical information completed as accurately as
possible, but should they not wish to do so any person can file a report on-line themselves. Doctors are not obliged to fill in report forms presented to them by patients and they do not have to send such reports to the FDA.

The site also contains information on safety issues and information on product recalls. It lists all products where there have been warnings, or other safety issues documented.

Recalls are actions taken by a firm to remove a product from the market. Recalls may be conducted on a firm's own initiative, by FDA request, or by FDA order under statutory authority. A Class I recall is a situation in which there is a reasonable probability that the use of or exposure to a violative product will cause serious adverse health consequences or death. A Class II recall is a situation in which use of or exposure to a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote. A Class III recall is a situation in which use of or exposure to a violative product is not likely to cause adverse health consequences.

A market withdrawal occurs when a product has a minor violation that would not be subject to FDA legal action. The firm removes the product from the market or corrects the violation. For example, a product removed from the market due to tampering, without evidence of manufacturing or distribution problems, would be a market withdrawal.

A medical device safety alert is issued in situations where a medical device may present an unreasonable risk of substantial harm. In some case, these situations also are considered recalls.
Appendix 3: Rare Cancers

The majority of cancers are rare cancers.
The National Cancer Institute (http://www.cancer.gov/) lists common cancers as:

<table>
<thead>
<tr>
<th>Bladder</th>
<th>Leukaemia</th>
<th>Non-Hodgkin’s lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>Lung</td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td>Melanoma</td>
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The list of all cancers includes these plus:

- Adrenocortical carcinoma
- AIDS-related lymphoma
- Anal cancer
- Astrocytoma
- Basal cell carcinoma
- Bile duct cancer
- Bone cancers
- Brain tumours – numerous types
- Carcinoid tumour
- Central nervous system lymphoma
- Cutaneous T-cell lymphoma
- Ependymoma
- Ewing’s tumours
- Extracranial germ cell tumour
- Extrahepatic bile duct cancer
- Eye cancers
- Gallbladder
- Gastric (stomach) cancer
- Germ cell tumours
- Gliomas
- Head and neck cancers
- Hepatocellular (liver) cancer
- Hodgkin’s lymphoma
- Hypopharyngeal cancer
- Hypothalamic and visual pathway glioma
- Islet cell (pancreatic) carcinoma
- Kaposi’s sarcoma
- Kidney (renal cell) cancer
- Laryngeal cancer
- Lip and oral cavity cancer
- Liver cancer
- Lymphomas
- Macroglobulinemia
- Medulloblastoma
- Mesothelioma
- Merkel cell carcinoma
- Multiple endocrine neoplasia
- Multiple myeloma
- Mycosis fungoides
- Myelodysplastic syndromes
- Nasal cavity and paranasal sinus cancer
- Nasopharyngeal cancer
- Neuroblastoma
- Oesophageal cancer
- Oral cancer
- Oropharyngeal cancer
- Osteosarcoma
- Ovarian cancer
- Pancreatic cancer
- Parathyroid cancer
- Penile cancer
- Pheochromocytoma
- Pineoblastoma
- Pituitary tumour
- Plasma cell neoplasm
- Pleuropulmonary blastoma
- Retinoblastoma
- Rhabdomyosarcoma
- Salivary gland cancer
- Sarcomas
- Sezary syndrome
- Skin cancers
- T-cell lymphoma
- Testicular cancer
- Thyroid cancers
- Transitional cell cancer of renal pelvis and ureter
- Urethral cancer
- Vaginal cancer
- Wilms’ tumour