Lecture 11

Organic Pharm. Chemistry for Pharmacy Students

By

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Course Outline
Drug discovery, design and development

- Choose a disease
- Choose a drug target
- Find a lead compound
- Isolate and purify the lead compound
- Identify the structure-activity relationships (SAR)
- Identify the pharmacophore
- Improve target interactions
- Improve pharmacokinetic properties

Course Outline
Drug discovery, design and development

- Patent the drug
- Preclinical trials
- Design a manufacturing process
- Clinical trials
- Register and market the drug
- **Make money**

Choose a disease

- A huge investment has to be made in the research and development of a new drug
- research projects tend to focus on diseases that are important in the developed world because this is the market best able to afford new drugs
- A great deal of research is carried out on ailments such as migraine, depression, ulcers, obesity, flu, cancer, and cardiovascular disease
- **Less research is carried out on the tropical diseases of the developing world ?!! (malaria, bellharsia**
- Science starts beyond this point

Choosing a drug target

- Drugs exert their action through interaction with their targets
- In the past targets were identified after discovery of their drugs, e.g. morphine.
- Drug targets are receptors, enzymes or nucleic acids
- Medicinal chemists should decide whether the desired effect is through the design of agonist or antagonist of receptor, or substrate or inhibitor for particular enzyme
- Drug targets identification showed excellent progress after mapping of human genome project

Choosing a drug target (contu….

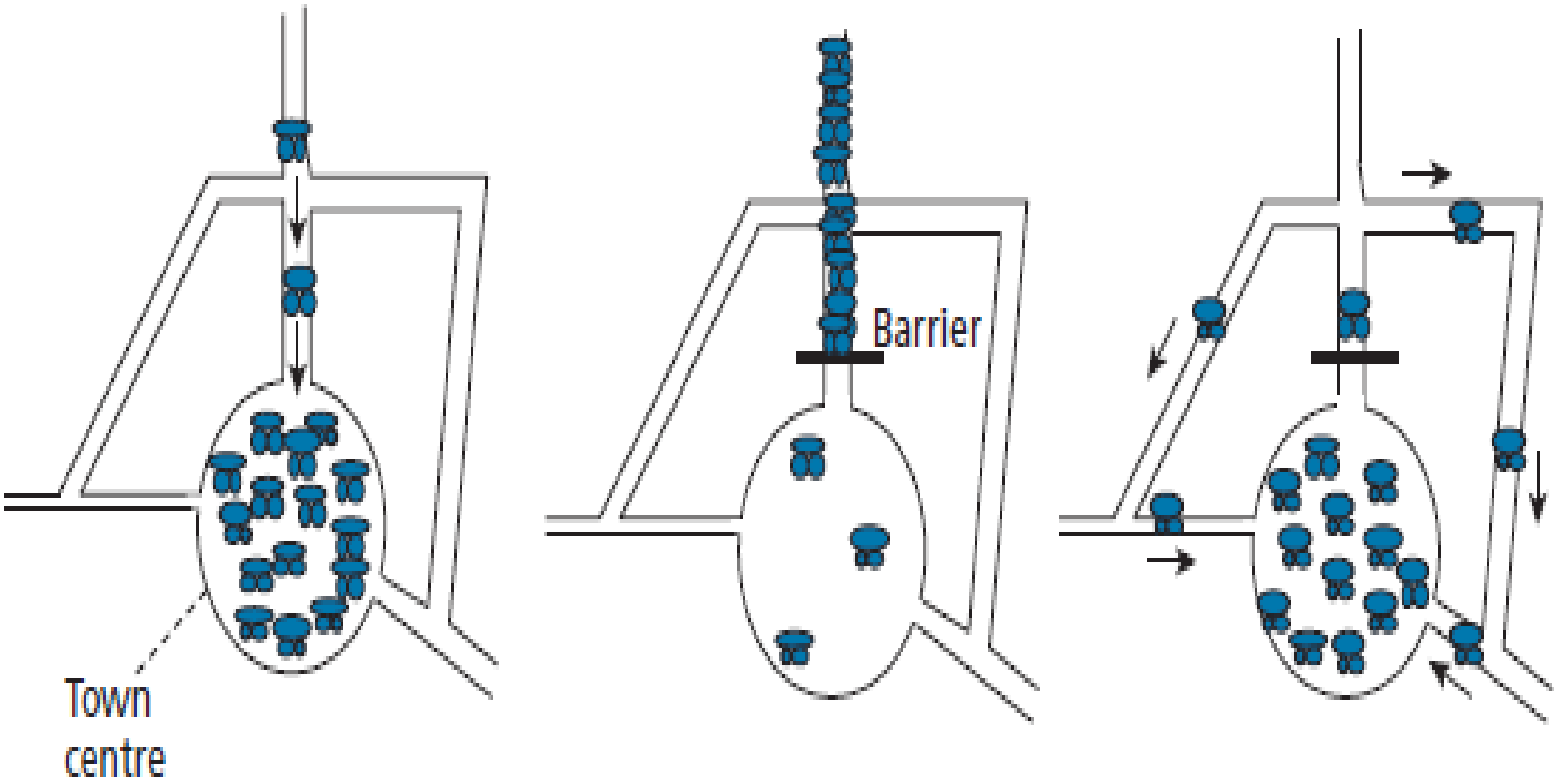
- **Target specificity and selectivity**
- Drug targets have different isoforms with different pharmacological actions
- The desired drug should act on the specific isoform
- Unwanted drug effects result often from the interaction of drug with other members of receptor or enzyme family
- Selectivity is one of the main challenges of drug design

Choosing a drug target (contu….

- In certain diseases, it is important to target different targets such as receptors, enzymes or ion channels
- Treatment of hypertension requires drugs with different targets such as beta receptors, angiotensin converting enzyme, angiotensin II receptors
- This is because cells have a highly complex system of signalling mechanisms, it is possible that the blockade of one part of that system could be overcome.

Choosing a drug target (contu….

- This could be compared to blocking the main road into town to try and prevent congestion in the town centre.
- The policy works, but, in a day or two, commuters discover alternative routes and congestion in the centre becomes as bad as ever

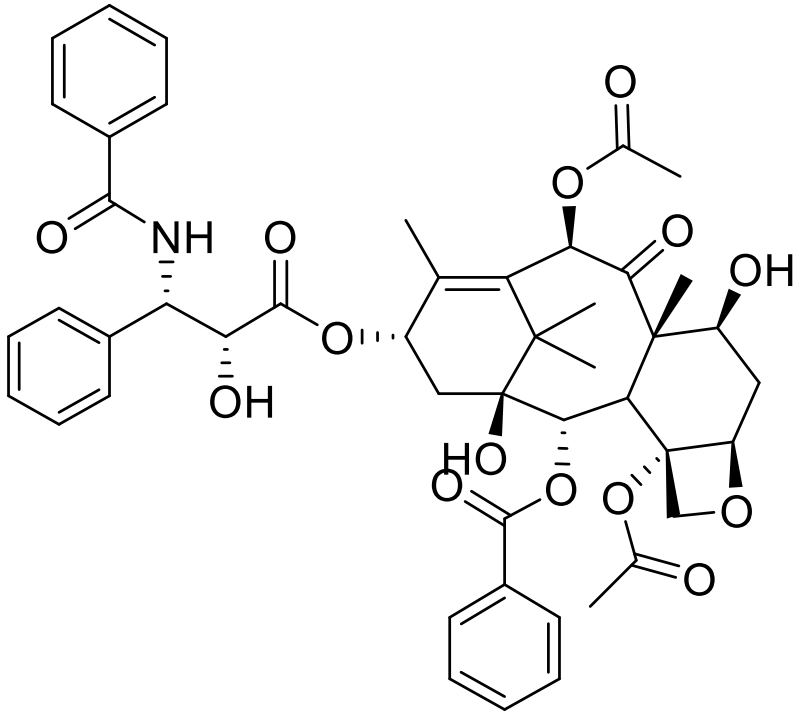

Barrier
Town
centre

Finding a lead compound

- The next stage of drug discovery project is finding a lead
- **Lead compound** is a compound which shows the desired pharmacological activity
- The level of activity may not be very great and there may be undesirable side effects, but the lead compound provides a start for the drug design and development process
- There are different ways for finding a lead compound

Finding a lead compound (contu…

- Screening of natural compound such as opioids (morphine, cocaine) and cholinergic drugs (tubocurarine, nicotine and muscarine)
- One of the most extensively studied natural anticancer drug is **taxol** from the yew tree



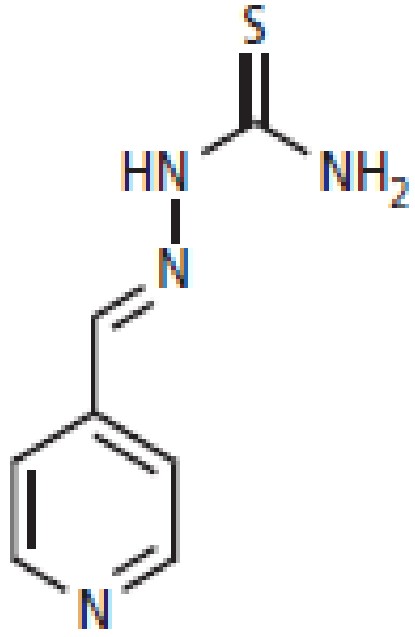
Finding a lead compound (contu…

- Screening of thousands of compounds synthesized by pharmaceutical companies are another source of lead compounds
- The main disadvantage of this source is that these compounds often represent small modifications of a common nucleus
- To overcome this, pharmaceutical companies try to diversify their range of structures by purchasing novel compounds prepared by research groups elsewhere—a useful source of revenue for university departments
- Th ese compounds may never have been synthesized with medicinal chemistry in mind and may be intermediates in a purely synthetic research project, but there is always the chance that they may have useful biological activity.

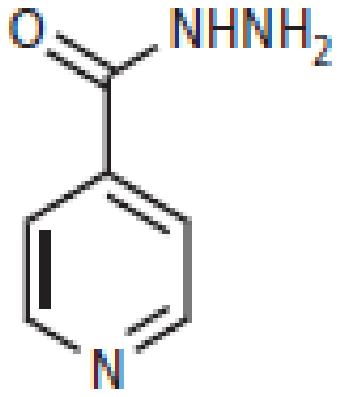
Finding a lead compound (contu….

- It can also be worth testing synthetic intermediates.
- **For example**, a series of thiosemicarbazones was synthesized and tested as antitubercular agents in the 1950s. These is included **isonicotinaldehyde thiosemicarbazone**, the synthesis of which involved the hydrazide structure **isoniazid** as a synthetic intermediate.
- It was found subsequently that isoniazid had greater activity than the target structure. Similarly, a series of **quinoline-3-carboxamide** intermediates were found to have antiviral activity

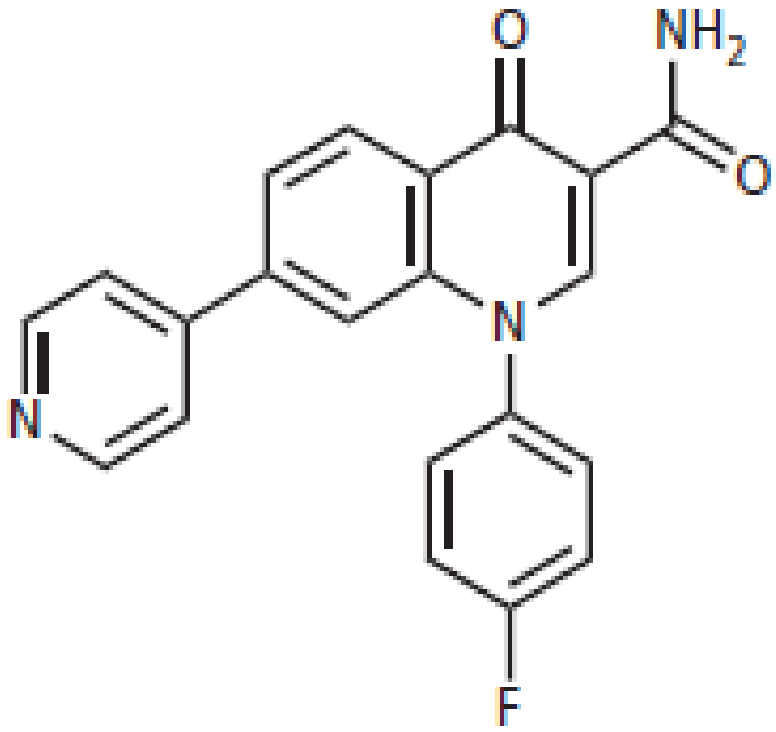
Finding a lead compound (contu…



Isonicotinaldehyde thiosemicarbazone



Isoniazid



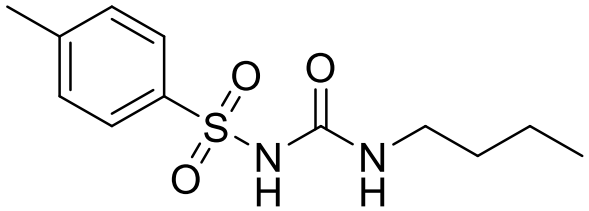
Quinoline-3-carboxamides

Finding a lead compound (contu..

- Lead compounds can be also obtained from existing drugs
- Sulfonamides have been used as antibacterial agents.
- Some sulfonamides with antibacterial activity could not be used clinically because they had convulsive side effects brought on by **hypoglycaemia**
- This is an undesirable side effect for an antibacterial agent, but the ability to lower blood glucose levels would be useful in the treatment of diabetes.
- Structural alterations were made to the sulfonamides concerned in order to eliminate the antibacterial activity and enhance antidiabetic activity

Finding a lead compound (contu..

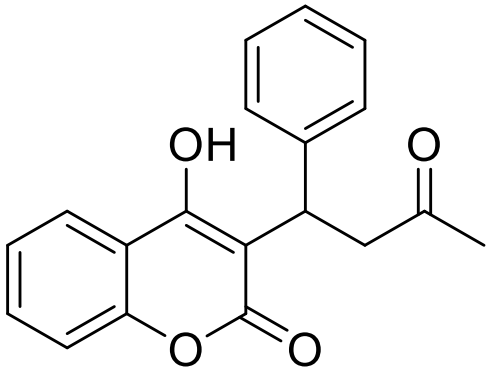
- This has led to the development of the antidiabetic sulfonamide tolbutamide



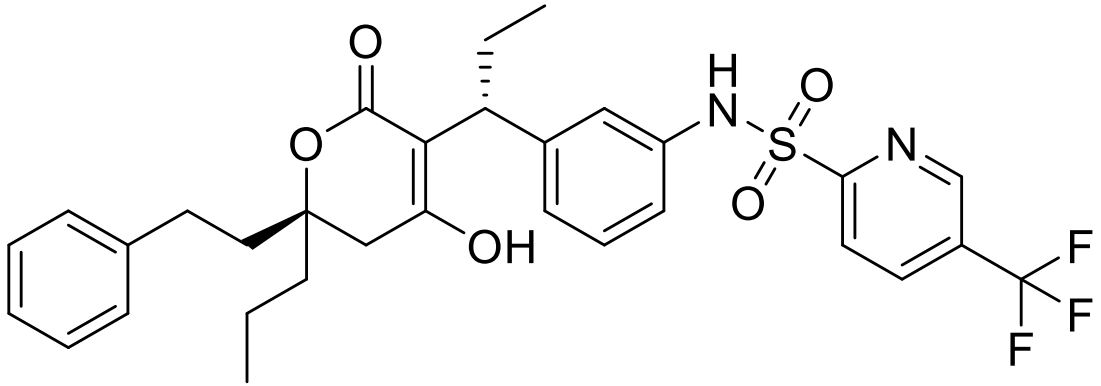
- the anticoagulant **warfarin** is also a weak inhibitor of a viral enzyme that is important in the life cycle of HIV.(Human Immunodeficiency virus)
- Warfarin was used as the lead compound in the development of an anti-HIV drug called **tipranavir**

Finding a lead compound (contu..

Lead Warfarin



warfarin



tipranavir

Getting the drug into the market

- There are various issues that need to be tackled before a promising-looking drug candidate reaches the clinic and goes into full-scale production
- The final phase is significantly more expensive in terms of time and money than either lead discovery or drug design, and many drugs will fall by the wayside.
- On average, **for every 10,000 structures synthesized during drug design, 500 will reach animal testing, 10 will reach phase I clinical trials, and only 1 will reach the market place**
- The average overall development **cost** of a new drug was recently estimated as **$800 million**

Drug metabolism studies

- The body has an arsenal ترسانة of metabolic enzymes that can modify foreign chemicals in such a way that they are rapidly excreted
- The structures formed from these reactions are called drug metabolites, and it is important to find out what metabolites are formed from any new drug
- The structure and stereochemistry of each metabolite has to be determined and the metabolite tested to see what sort of biological activity it might have

Pharmacology, formulation, and stability tests

- It is usually necessary to carry out more tests to see whether the drug has **activity** at targets other than the intended one, and to gain a better insight into the drug's mechanism of action
- These studies also determine a dose–response relationship and define the drug's duration of action
- **Formulation** studies involve developing a preparation of the drug which is both stable and acceptable to the patient
- For orally taken drugs, this usually involves incorporating the drug into a tablet or a capsule

Pharmacology, formulation, and stability tests

- **Pre-formulation** involves the characterization of a drug's physical, chemical, and mechanical properties in order to choose what other ingredients should be used in the preparation
- **Formulation studies** then consider such factors as particle size, salt forms, crystal polymorphism, solvates, pH, and solubility, as all of these can influence **bioavailability** and, hence, the activity of a drug
- The drug must be combined with inactive additives by a method which ensures that the quantity of drug present is consistent in each dosage unit
- **The dosage** should have a uniform appearance, with an acceptable taste, tablet hardness, or capsule disintegration.

Preclinical testing

- **Toxicity testing**
- One of the first priorities for a new drug is to test if it has any toxicity
- This often starts with *in vitro* tests on genetically engineered cell cultures and/or *in vivo* testing on transgenic mice to examine any effects on cell reproduction and to identify potential carcinogens
- **Any signs of carcinogenicity would prevent the drug being taken any further**

Clinical trials

- **Phase I studies**
- Phase I studies take about a year and involve 100–200 volunteers
- They are carried out on healthy human volunteers to provide a preliminary evaluation of the drug's safety, its pharmacokinetics, and the dose levels that can be administered, but they are not intended to demonstrate whether the drug is effective or not
- In situations where the drug is potentially toxic and is to be used for a life threatening disease, such as AIDS or cancer, volunteer patients are used for phase I studies rather than healthy volunteers

Clinical trials

- **Phase II studies**
- Phase II studies generally last about two years and may start before phase I studies are complete
- They are carried out on patients to establish whether the drug has the therapeutic property claimed, to study the pharmacokinetics and short-term safety of the drug, and to define the best dose regimen
- Most phase II trials require 20–80 patients per dose group to demonstrate **efficacy**

Clinical trials

- **Phase III studies**
- Phase III studies normally take about three years
- These studies may begin before phase II studies are completed
- The drug is tested in the same way as in phase II, but on a much larger sample of patients
- Patients taking the drug are compared with patients taking a placebo or another available treatment
- Comparative studies of this sort must be carried out without bias and this is achieved by randomly selecting the patients—those who will receive the new drug and those who will receive the alternative treatment or Placebo

Clinical trials

- Serious side effects observed during phase III may result in early **termination** of the clinical trials and the stopping of further development
- For example, the development of Pfizer's **torcetrapib** (a cholesterol-lowering agent) was terminated in 2006 when it was discovered that there was a statistically increased risk of death associated with its use
- The drug had been **developed over a period of 16 years at a cost of $800 million** and represented one of the costliest failures in pharmaceutical history

Clinical trials

- **Phase IV studies**
- Th e drug is now placed on the market and can be prescribed, but it is still monitored for effectiveness and for any rare or unexpected side effects
- In a sense, this phase is a never-ending process as unexpected side effects may arise many years after the introduction of the drug
- The β-blocker **practolol** had to be withdrawn after several years of use because some patients suffered blindness and even death

Clinical trials

- **Rofecoxib** (VIOXX) was used to treat rheumatoid arthritis for five years before a clinical trial carried out after its release showed that it was associated with increased risks of heart attack and stroke
- The drug was withdrawn voluntarily by Merck in 2004, but in the 5 years it had been on the market, rofecoxib had been prescribed to 1.3 million patients in the USA and to 700,000 patients in 80 other countries
- Annual profits from the drug had reached $1.2 billion, which represented 18% of Merck's net income

Clinical trials

- The loss of this income was so serious that the company's share price dropped 27% in value in a single day
- Not only that the company was faced with a lengthy litigation battle as thousands of patients sought compensation for claimed personal injuries resulting from the use of the drug

Patenting

- Having spent **enormous amounts of time and money** on research and development, a pharmaceutical company wants to get the benefit of all its hard work
- It needs to have the exclusive rights to sell and manufacture its products for a reasonable period of time, and at a price which will not only recover its costs, but that will generate sufficient profits for further research and development
- Without such rights, a competitor could synthesize the same product without suffering the expense involved in designing and developing it

Patenting

- **Patents in most countries run for 20 years** after the date of filing
- This sounds a reasonable time span, but it has to be remembered that the protection period starts from the time of filing, not from when the drug comes onto the market
- A significant period of patent protection is lost because of the time required for preclinical tests, clinical trials, and regulatory approval which involves a period of 6–10 years
- The income obtained from a successful drug is so important to a company's financial viability that **pay-for delay deals** have become a growing trend in the pharmaceutical sector for drugs that are nearing the end of their patent lifetime

Patenting

- These involve a pharmaceutical company making a deal with a manufacturer that specializes in producing generic drugs
- The generic manufacturer receives a huge amount of money if it agrees to delay manufacturing the generic version for an agreed time period (typically a year), allowing the inventor to gain several months of additional income

The regulatory process

- Before clinical trials can begin, the company has to submit the results of its scientific and preclinical studies to the relevant regulatory authority (**FDA for USA**)
- The FDA assesses this information and then decides whether clinical trials can begin
- Dialogue then continues between the FDA and the company throughout the clinical trials
- Any adverse results must be reported to the FDA, who will discuss with the company whether the trials should be stopped

Regulatory process

- If the clinical trials proceed smoothly, the company applies to the regulatory authority for marketing approval
- In the USA, this involves the submission of a **New Drug Application** (**NDA**) to the FDA
- An NDA is typically 400–700 volumes in size, with each volume
- containing 400 pages ملف الدواء الجديد
- The application has to state what the drug is intended to do, along with scientific and clinical evidence for its efficacy and safety

Regulatory process

- It should also give details of the chemistry and manufacture of the drug, as well as the controls and analysis which will be in place to ensure that the drug has a consistent quality
- Any advertising and marketing material must be submitted to ensure that it makes accurate claims and that the drug is being promoted for its intended use
- **The labelling** of a drug preparation must also be approved to ensure that it instructs physicians about the mechanism of action of the drug, the medical situations for which it should be used, and the correct dosing levels and frequency
- Possible side effects, toxicity, or addictive effects should be detailed, as well as special precautions which might need to be taken

Analysis of cost versus benefit

- The last barrier for the drug to reach the market is the cost versus benefit analysis by the government authority
- the UK's **National Institute for Health and Clinical Excellence** (**NICE**) determines whether novel drugs should be used by the National Health Service (NHS) and have rejected several approved anticancer drugs, such as **lapatinib**, **dasatinib**, **sorafenib**, **nilotinib**, **bevacizumab**, and **temsirolimus**
- The decisions of NICE have a significant economic impact on world-wide pharmaceutical sales, as more than 60 other countries adopt the NICE guidelines