# Drug Development

Bringing medicines to life

British Neuroscience Association

BNA is a registered charity (no. 1103852)

**Background**

The aim of this session is to introduce students (aged 12-18) to the drug development process. Students will have the opportunity to discuss what they already know about the process, learn all the steps and ask any questions they may have. This information sheet should be used in conjunction with the 'Secondary– Drug Development PPT' PowerPoint presentation.

## From lab to shelf

**(Slide 1)** Title slide **(2)** Start by asking the students what they know about drug development and allow time for discussion. Drug development is defined as the discovery, validation and, finally, production of medicines. Then ask the students 'how long do you think drug development takes?'

Take suggestions. The development of a drug can take up to 15 years and has different phases: drug discovery, preclinical trials and finally clinical trials with human volunteers.

## Drug discovery

**(3)** Start by asking the students where they think drug discovery happens. The answer is at the laboratory bench of a university or research centre. Researchers funded by the government and pharmaceutical industries try to answer different biological questions and understand health and disease. Years and years of studies help to identify some potential targets. Targets are, as an example, genes or proteins causing a disease or condition.

**(4)** Once a potential target is identified, researchers look for a molecule or compound that will act upon this target. You can explain how a drug acts upon a target using an example, such as codeine, an opioid used as a pain killer:

Researchers identified that one type of protein, a receptor, is always activated in a disease. Receptors are proteins located in the membranes of cells, which separate the outside and inside of cells. In the extracellular part, receptors have a 'pocket' in which they bind compounds that affect their activation (ligands).

As an example, the receptor identified as a target is located in the synapse of neurons involved in pain sensation. If you want to stop feeling pain, you can target the receptor. Ask the students how they could target the receptor. Take suggestions.*

*See final page of sheet

Roche This activity has been supported by a grant from Roche Products Ltd

Then, explain that receptors can bind different ligands, some activate and some block the receptor. The drug target will be the receptor and we will need to find a ligand that binds to the receptor and blocks its activation.

**(5)** Usually, researchers use compounds from plants, fungi, bacteria and animals. Ask the students to think about drugs we use that come from other organisms (as an example, penicillin that comes from fungi). New scientific discoveries introduced the use of genetic engineering and the creation of synthetic compounds.

Usually, at this stage, researchers consider 5000-10000 potential compound candidates.

## Pre-clinical or Phase 0

The compounds need to be tested for safety and efficacy before being tested in humans. Ask the students how they think drugs are tested. Take suggestions.

**(6)** In vitro using cells and tissues, computer modelling and animal testing are used in the drug discovery and pre-clinical stages. Refer to the module in 'Animals in neuroscience research' if you need more information about their use in drug development.

However, humans can participate in this stage to study the behaviour of the drug, using a method called microdosing. Microdosing uses very low doses of the drug to see their effect, reducing time and money invested in non-viable drugs and number of animals. Approximately 10-20 candidates show promising results.

**Advanced information:**

Where the drug is going to be delivered (target region) is extremely important to consider when designing a drug. Neuroscientists trying to target diseases in the brain face an extra problem, the brain has a border called the **Brain Blood Barrier** or BBB. The BBB separates the circulating blood in our body from the brain and only certain molecules are allowed to cross it. These are very small molecules and compounds the brain need to function, such as glucose and water.

When the preclinical studies end, pharmaceutical companies will send a clinical trial proposal to the appropriate authorities.

A panel of scientists and medical experts evaluate the proposal. If accepted, clinical trials will start.

## Clinical trials: 3 phases

**(7)** Participation is voluntary and volunteers are monitored and assessed continuously. The clinical trial is divided into different phases:

- Phase I: A small group of healthy volunteers (20-100) receive a range of doses of the compound to confirm the safety in humans.
  Half of the compounds tested fail in this stage, from the initial 10-20 candidates, only 5-10 show promising results.
- Phase II: A group of volunteer patients (100-300) receive the compound. The aim is to assess effectiveness, the best dose and delivery method (oral, intravenous). Additionally, phase II reconfirms safety.
  Most drugs fail phase II because of ineffectiveness, safety problems and/or intolerable side effects. Only 2-5 continue.
- Phase III: A large number of volunteer patients (1000-5000) from multiple different locations. Ask the students 'Why do you think compounds are tested on people from different locations?'. The aim is to reconfirm phase II findings, identify the best dosage regimen and demonstrate safety and efficacy to the authorities. Only 1-2 drugs successfully pass.

Do not mention the placebo effect when describing/ performing the below activity otherwise the demonstration is unlikely to work.

## The placebo effect

**(8)** This activity will show the placebo effect and the students will learn why it is important to consider it when designing a clinical trial.

Before starting, ask for volunteers (this will represent the use of volunteers in clinical trials) and inform them about the experiment. The experiment will consist in testing an analgesic cream with a compound that reduces pain sensation. To test it, volunteers will put their hand in icy water.

**(9)** Volunteers need to be informed and understand what the procedure consists of and any possible side effects. You need to mention that people with very sensitive skin should avoid participating. This represents the consent form that volunteers sign.

Then, ask the students how they feel pain. The pain receptors are on the skin, formed by the ends of sensory neurons. These neurons, in the response of a stimulus, such as a very cold sensation, send a signal to the spinal cord and the brain that, in turn, will make our hand move away.

Once you've explained the experiment, divide those who have agreed to take part into two groups (easiest way is by giving them either the number 1 or 2), telling one group that they'll be using the 'analgesic cream' and the other that they'll just have normal cream. Then the 'clinical trial' can start.

Firstly, instruct volunteers to put one hand inside of a bucket with water and ice and take it out when the sensation starts to feel too unpleasant. Non-volunteers can act as researchers using a stopwatch to measure the 'pain threshold' (the time they can hold the hand inside the water) and take notes.

Secondly, give one group the 'analgesic' cream, the other the normal ordinary cream. They should wait two minutes for absorption time to reveal the 'effect'. Then, instruct the students to repeat the same experiment with putting their hands in icy water and recording their pain thresholds/the duration of time they can keep their hand in the water for.

Finally, compare the results. Did the group with the 'analgesic cream' perform better this time? (longer pain threshold).

**(10)** Finally, show that both creams are the same with no analgesic properties. The placebo effect causes the differences observed. The *placebo effect* is considered to be a psychological phenomenon. It occurs when a patient receives a non-effective treatment but reports a response. For this reason, clinical trials include control groups with a 'fake' pill to test the placebo effect.

Introduce the placebo effect as a possible problem to consider when designing a clinical trial.

Try to make the activity more credible using real containers. For example, the normal cream can be the hypoallergenic E45 moisturising lotion from a drugstore, and the pain-reducing one can be the same one in a real anaesthetic cream container.

## Licensing

**(11)** Ask students 'What happens after a drug successfully makes it through phase III?'

The pharmaceutical company must apply to the appropriate authorities to produce and market the drug. But, this is not the end of the process:

- In England and Wales, the national institute of Health and Care Excellence (NICE) is responsible for making this new drug available to the NHS. They will make a decision based on the efficacy and cost (it is affordable?).
- Clinical trials may continue (phase IV) to assess long term effects (pharmacovigilance), to test their use in combination with other drugs or in patients with different conditions (as an example in pregnant women), etc.

## Patenting

**(12)** Annually, the pharmaceutical industry invests hundreds of billions of pounds to develop new medicines that will change the lives of patients. The process to develop a new drug takes 10-15 years and many drugs fail during the process.

Producing new medicines has a huge fail rate and is highly risky. Patents allow pharmaceutical companies to recoup investments made for drug development and where most drugs fail, invest in new medicines and make profit.

Pharmaceutical companies will patent any promising molecules/compounds/techniques to avoid other companies copying their results. A patents lasts 20 years, and once it has expired, generic versions can be produced. By the time a drug has undergone the required testing and been licensed, half the patent period will usually have expired.

.....

**(13)** To finish, recap all the information presented with a final slide and **(14)** answer any questions.

*An activity to illustrate this concept

When talking about targets and receptors on slide 4, you could give the students an object which has a hole/indentation in it, e.g. a cookie cutter, tub etc as well as some modelling clay/play dough etc. You could tell the students to imagine that the object is the receptor. When you ask them how they might target the receptor to give pain relief, you can ask them to show you with what you've given them. Hopefully students will produce a 'ligand' from the modelling clay and you can discuss the fact that the drug will be a ligand that blocks activation of the receptor. This activity can be useful for discussing how drugs have to be the correct shape and have the correct properties to bind to the receptor and block its activation.