Researchers in Schools

Discovering Drugs:

The Design and Development of Medicines

Pupil Name	
Coursebook Designed by	Dr J. Devonport

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Timetable and Assignment Submission

Timetable – Tutorials

Tutorial	Date	Time	Location
1			
2			
3			
4			
5			
6 (Feedback)			
7 (Feedback)			

Timetable – Homework Assignments

Homework Assignment	Description	Due Date
Tutorial 1	Baseline Assignment – Comparing Drugs	
Tutorial 2	Penicillin Research	
Tutorial 3	The Importance of Pre-clinical Testing	
Tutorial 4	Animal Testing Poster	
Tutorial 5	Final Assignment – The Process of Drug Design	

Assignment Submission – Lateness and Plagiarism

Lateness	
Submission after midnight on due date	10 marks deducted
Plagiarism	
Some plagiarism	10 marks deducted
Moderate plagiarism	20 marks deducted
Extreme plagiarism	Automatic fail

Course Rationale

It could be argued that the most important application of science to human health is the discovery and development of drugs capable of treating diseases. Some of the largest and wealthiest companies that exist today are pharmaceutical companies founded on the core principle of discovering, testing, and distributing new medicines. It could be said you would be financially better off discovering the cure to cancer compared to discovering an actual gold mine!

A medicine is a type of drug that affects the body by curing disease or relieving suffering. They do this by interacting with biochemical processes that occur inside cells and are associated with the disease. Humans have discovered and developed cures and treatments for many diseases, however, some remain incurable such as Alzheimer's disease and many types of cancer. Therefore, there remains great global interest in the discovery and development of new medicines. The current COVID-19 pandemic has bought revived attention to drug discovery with the rapid discovery and distribution of COVID-19 vaccinations. Whilst this should serve as an exemplary model of how far modern drug development has come since the discovery of penicillin by Alexander Fleming in 1928, many remain fearful of vaccines. The current 'anti-vax' movement and fear of modern medicine can largely be attributed to a lack of understanding in the process of drug development and the science it is founded on.

In this course, we will study how scientists discover and develop drugs so that they are safe and effective for use by medical doctors.

We will look at the answers to some of the key questions about drug development:

- What are medicines made from?
- How does a scientist know if a drug is a medicine?
- How does a scientist know if a drug is safe or not?
- Why are animals experimented on during drug development?
- How do scientists test potential medicines in humans?

Uni Pathways Mark Scheme 2021 – science-based assignments

	Subject Knowledge	Critical Thinking	Written Communication
1st	The work shows a depth of knowledge and understanding of key concepts and scientific methods, through engaging with relevant sources. Knowledge is used to build and support highly effective scientific arguments and explanations.	Analyses key scientific evidence, arguments, and reasoning. Interprets meaning and makes connections. Identifies and critically evaluates key scientific arguments and evidence, deciding on their credibility, strength, and relative significance, drawing convincing conclusions.	The work has a coherent flow and is well structured. The writing style is appropriate; scientific language and key scientific terms are used accurately and effectively to support the arguments and explanations made. There are no, or very few, errors in spelling or grammar. Consistent referencing, appropriate paragraphing and use of correctly labelled tables and graphs matching the style taught in the course.
2:1	The work shows an understanding of key concepts and scientific methods, drawing on relevant sources. Knowledge is used to build and support effective scientific arguments and explanations.	Analyses relevant scientific evidence, arguments, and reasoning. Identifies and critically evaluates relevant scientific arguments and evidence, deciding on their credibility and strength, drawing reasonable conclusions. Shows some understanding of the relative value of evidence and arguments.	The work is well-structured. The writing style is appropriate; scientific language and key terms are used correctly. There are a few errors in spelling or grammar. Mostly consistent referencing and use of tables and figures; matching the style taught in the course.
2:2	The work shows an understanding of key concepts and scientific methods, with no major misconceptions. Beginning to apply this knowledge to build and support effective scientific arguments and explanations.	Identifies and uses basic scientific evidence, arguments, and reasoning. Showing some understanding of the quality of scientific arguments and evidence. Not yet showing understanding of the relative value of evidence and arguments.	The work has some structure. The writing style can sometimes be informal; occasionally scientific language and key terms are not used when it would be appropriate to do so. There are some errors in grammar and spelling that do not get in the way of communicating the content. Referencing has some consistency; matching the style taught in the course Limited use of tables and graphs.
3rd	Shows a developing understanding of key concepts and scientific methods, with some misconceptions. Does not yet apply this knowledge to build and support scientific arguments and explanations.	Beginning to analyse scientific evidence, arguments, and reasoning. Describes evidence and arguments, while not yet evaluating them.	The grammar, spelling, style, and structure of the work need improving to communicate ideas to the reader. Scientific language, key terms and references are not always used correctly. Limited, or no use of tables and graphs.

Baseline Assignment (essay based): Pupil Feedback Report

Name of Pupil	
Name of School	
Name of RIS teacher	
Title of Assignment	

How your assignment is graded:

Grade	Marks	What this means
1st	70+	Performing to an excellent standard at A-level
2:1	60-69	Performing to a good standard at A-level
2:2	50-59	Performing to an excellent standard at GCSE
3rd	40-49	Performing to a good standard at GCSE
Working towards a pass	0-39	Performing below a good standard at GCSE
Did not submit	DNS	No assignment received by The Brilliant Club

Lateness	
Any lateness	10 marks deducted
Plagiarism	
Some plagiarism	10 marks deducted
Moderate plagiarism	20 marks deducted
Extreme plagiarism	Automatic fail

Marks

OVERALL MARK / 100		FINAL MARK / 100 (including any deductions)	
DEDUCTED MARKS		FINAL GRADE	

If marks have been deducted (e.g. late submission, plagiarism) the teacher should explain in this section:

Mark Breakdown and Feedback

Subject knowledge	
	mark
Critical thinking	
	mark
Written communication	
	mark

Final Assignment (essay based): Pupil Feedback Report

Name of Pupil	
Name of School	
Name of RIS teacher	
Title of Assignment	

How your assignment is graded:

Grade	Marks	What this means
1st	70+	Performing to an excellent standard at A-level
2:1	60-69	Performing to a good standard at A-level
2:2	50-59	Performing to an excellent standard at GCSE
3rd	40-49	Performing to a good standard at GCSE
Working towards a pass	0-39	Performing below a good standard at GCSE
Did not submit	DNS	No assignment received by The Brilliant Club

Lateness	
Any lateness	10 marks deducted
Plagiarism	
Some plagiarism	10 marks deducted
Moderate plagiarism	20 marks deducted
Extreme plagiarism	Automatic fail

Marks

OVERALL MARK / 100		FINAL MARK / 100 (including any deductions)	
DEDUCTED MARKS		FINAL GRADE	

If marks have been deducted (e.g. late submission, plagiarism) the teacher should explain in this section:

Mark Breakdown and Feedback

Subject knowledge	
	mark
Critical thinking	
	mark
Written communication	
	mark

Launch Event

The launch event is your opportunity to learn more about this course and Uni Pathways. You will watch some videos, listen to your teacher and have some discussion. Below is some room to make notes for some of the videos you will watch during the event.

Virtual Campus Tours

Notes…

The Scholars Programme Alumni

Notes…

Student Ambassadors

Notes…

Subject Vocabulary

Word	Definition	In a sentence
Drug	A drug is a substance that affects the body. e.g., Paracetamol or Alcohol.	People take drugs because of their effect on their bodies.
Recreational	Something done for enjoyment. e.g. gaming.	Football is a recreational activity.
Illegal	Not allowed by the law; not legal.	It is illegal to be in possession of Class A drugs.
Medicine	A substance that treats disease and aids in suffering.	Paracetamol is a medicine as it helps with my headaches.
Prescription drug	A medicine that can only be given (prescribed) to you with a doctor's permission.	Antibiotics are usually prescription drugs and can only be prescribed by doctors.
Physiological effect	A fancy science way of saying it influences the function of an organism.	Alcohol has a physiological effect and that's why people get drunk.
Drug development	The process of making and testing new medicines so that they are safe and effective.	Drug development is key to making sure new medicines are safe.
Drug design	The process of identifying and isolating substances that have the potential to be medicines.	Thanks to drug design many new medicines have been invented.
Drug candidate	The substance identified to have potential to become a medicine.	Computers can be used to identify new drug candidates.
Drug target	Usually, a protein that influences disease that a drug aims to affect to alter the disease.	Many proteins are responsible for cancer meaning there is no specific drug target for design.
'Anti-vaxxer'	Someone who believes that vaccines are dangerous and refuses their use because of their lack of scientific understanding.	Anti-vaxxers are spreaders of false information.
Natural drugs	Drugs that are sourced and purified from natural sources, e.g., Aspirin from willow bark or penicillin from mold.	People used to chew willow bark for pain relief as it contained a natural drug.
Synthetic drugs	Man-made drugs that are synthesised using chemicals rather than natural ingredients.	Paracetamol is a common synthetic drug.

Efficacy	How effective a medicine is at affecting its biological target.	Many drugs do not progress through clinical trials due to lack of efficacy.
Cell assay	A method of testing drugs on individual cells before testing them on whole organisms.	The latest anti-cancer drug successfully killed all the cancer cells in my cell assay and now will be tested in whole organisms.

Tutorial 1 – What Are Drugs?

What is the Purpose of Tutorial 1?

- Define what a 'drug' is.
- Be able to organise different types of drugs into categories.
- To understand the importance and purpose of medicines.

Activity 1:

- On a post-it note write what you think a drug is. On a separate post-it give 3 different examples of substances that you think are drugs.
- Share your knowledge! Come and stick your post-it up on the board.

Activity 2:

What is the correct definition of a 'drug'?

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What are the 3 different categories of drugs?

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Give 2 reasons why you think people may want to take a drug?

- 1:
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  ……
- 2:
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Categorise the drugs below as either Medicinal, Recreational, or Illegal.

Drug	Type
Paracetamol	
Nicotine	
Caffeine	
Alcohol	
Heroin	
Ibuprofen	
Penicillin	
Cannabis	
Antihistamines	

Activity 3:

A medicine can be defined as a treatment for illness or injury' – **Cambridge Dictionary**

Below list as many different medicinal drugs as you can think of!

Tutorial 1 Notes:

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Homework

Baseline assignment:

Give one example of a pharmaceutical drug and one example of a recreational drug. Explain how they affect the body and why people take them. (approx. 200-300 words)

Details of the assignment:

Pick one example of a pharmaceutical drug (medicine) and one example of a recreational drug.

Try to mention how each drug affects the body and the reasons people take it.

Try to break your answer down into different subsections. For example:

- Introduction (20-30 words)
- Drug A (c. 50 words)
- Drug B (c. 50 words)
- Conclusion (20-30 words) (try to compare Drug A and Drug B)

Success criteria – how to structure your assignment and what to include:

A great assignment will include the following:

- Good use of subsections (see above).
- The definition of what a drug is.
- One example of a pharmaceutical drug.
- One example of a recreational drug.
- Summary of the effects of the example drugs.
- Comparisons between the two examples based on their effect and use.

In this assignment, show me that you **understand**:	Show me that you **are able to**:
What drugs are. There are different types of drugs. That drugs have different effects on the body.	Recognise the difference between medicines and recreational drugs. Recognise that they have different effects on the body and therefore are taken for different reasons.

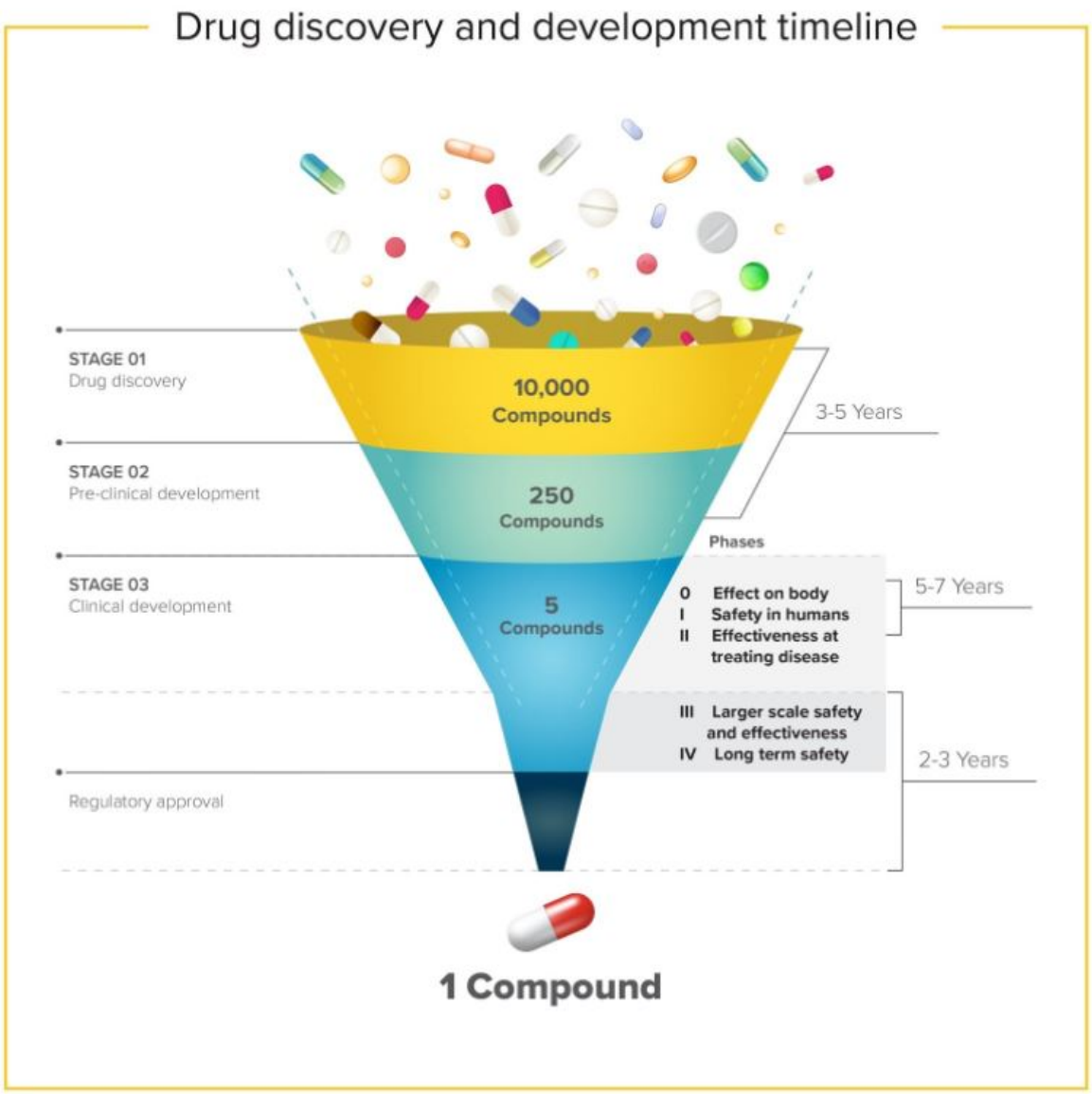
Tutorial 2 –How Do We Discover New Drugs?

What is the Purpose of Tutorial 2?

- To summarise the different stages of drug development.
- To explain what is meant by a 'drug target'.
- To describe the different ways potential drug candidates are identified.

Activity 1:

Listen to the teacher's explanation and use the following image to answer the questions about drug development below.



From design to distribution, how long is the drug development process in total?

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What stage of drug development takes the longest?

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On average how many compounds are discovered in the discovery stage?

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What is the estimated cost of development for a single drug?

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Explain why so few drugs end up achieving regulatory approval?

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Activity 2:

Match each drug with the correct target.

Drug	Target
Drug for Cancer treatment	Drebin protein: Responsible for hallucinations in the brain
Drug for Alzheimer's disease treatment	Bromodomain Protein: Responsible for excess cell division
Drug for COVID-19 treatment	Amyloid Beta protein: Protein responsible for memories in neurones
Drug for the schizophrenia	Spike protein: Responsible for recognition of Viruses
Drug for the heart disease	C-reactive protein: Responsible for maintenance of heart cells

Activity 3:

Explain what is meant by the term 'Synthetic Drug'?

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Explain what is meant by the term 'Naturally Derived Drug'?

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Fill in the vocabulary table below with the new terms:

Word	Definition	In a sentence
Computer-based design		
High throughput screening		

Tutorial 2 Notes:

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Homework:

Use **Appendix 3** and your own sources (websites, books, news articles etc…) to research the discovery of penicillin and answer the questions below:

Who discovered penicillin and in what year?

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What type of drug is penicillin and what is used to treat?

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Describe how penicillin was discovered and state whether it is a naturally derived medicine or a synthetic medicine.

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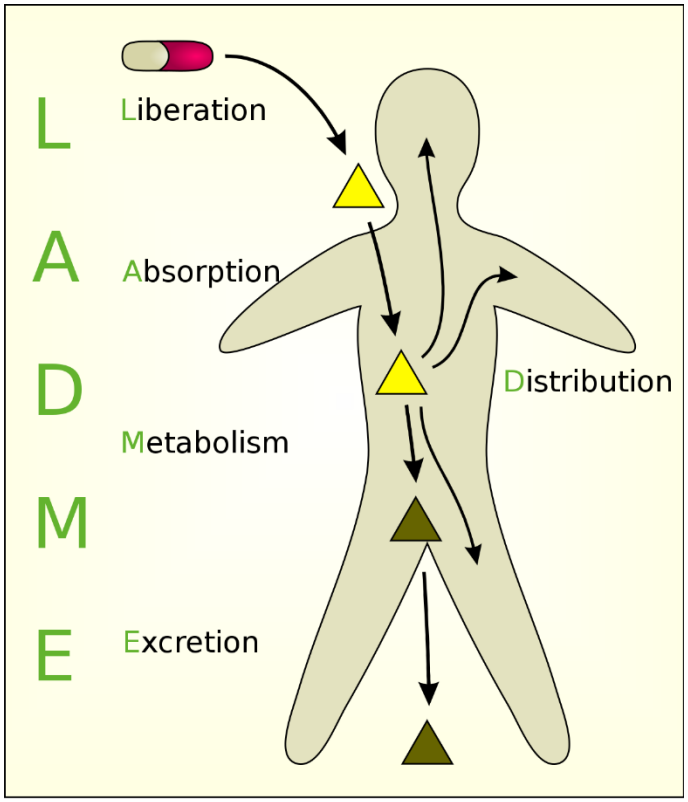
Success Criteria

- Good use of own research to investigate how penicillin was discovered.
- State whether penicillin is a natural or synthetic medicine.
- State who discovered penicillin and when (date).
- State what penicillin is used to treat.

Tutorial 3 – How Do We Improve Drug Candidates?



What is the Purpose of Tutorial 3?

- To explain why scientists will modify drugs in development.
- To describe what constitutes an ideal drug candidate.
- To describe how drugs are tested in the preclinical stage.

Activity 1:

A medicinal chemist will modify the chemical structure of drug candidates to improve certain properties. This process can take a very long time and is very expensive but is important to make sure drugs are suitably safe and effective.

In the table below explain the importance of each property in terms of drug development. How would a medicinal chemist want to modify a drug to improve on that property?

Drug properties	**Effect on drug development**
Metabolic stability: *A measure of how stable a drug is in the body. Poor metabolic stability means a substance is rapidly metabolised (broken down) in the body into smaller substances.*	
Solubility: *A measure of how much of the drug can be dissolved in water. For example, sugar is highly soluble whereas sand is insoluble.*	
Permeability: *Permeability is a measure of a substances ability to pass through cell membranes and move into the cell.*	
Excretion profile: *How long the drug stays in the body before being excreted in the urine or faeces.*	
Toxicity: *Toxicity is how harmful a substance is to cells and organisms. Cyanide is highly toxic.*	

Activity 2:

Three new drug candidates have undergone pre-clinical studies using cell assays. Below are the findings.

In pairs, discuss the properties of the two drugs below. What needs to be improved before the drugs can progress to the next stage of development?

Cureitallicillin

- Low metabolic stability: Rapidly breaks down to smaller, ineffective, substances.
- Non-toxic: Does not kill cells in preliminary studies.
- Very soluble in water.
- Excreted in the urine after a reasonable time.
- Poor permeability through cell membranes in cell studies.

Feelbetteramide

- High metabolic stability: Is excreted without being metabolised to smaller substances.
- Some toxicity: Kills some cells but not all in studies.
- Very soluble in water.
- Excreted in the faeces after only a few minutes.
- Good permeability though cell membranes.

Toxicillin

- High metabolic stability: Is excreted without being metabolised to smaller substances.
- Highly toxic: Kills cells in all studies.
- Not soluble in water at all.
- Never excreted from the body.
- Good permeability though cell membranes.

Word	Definition	In a sentence

Tutorial 3 Notes:

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Homework:

Explain why it is important to test drug candidates in cell models before testing them in live organisms.
What would be the risk if we tested all drugs in live organisms straight away?

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Give your own criteria (rules) that you think every drug candidate should meet before it can be tested in live organisms. Use of bullet points is encouraged.

Success Criteria

- Discuss the risks of using untested drugs in live organisms.
- State criteria that potential drugs should meet before testing in animals.

Tutorial 4 – Why Do Scientists Test Drugs on Animals?

What is the Purpose of Tutorial 4?

- To understand why animal testing is used in drug development.
- To identify some of the animals commonly used in animal research.
- To discuss some of the ethical, moral and financial considerations of animal testing.

Activity 1:

- On a post-it note write down what you think of when you hear the phrase 'animal testing'. You can use more than one post-it note if you wish.
- Stick your post-it notes on the board and be ready to discuss.

Activity 2:

Use the information given by the teacher or from the videos you have been shown to answer the questions below.

The '3 Rs' are principles designed by scientists to improve animal welfare and scientific accuracy. Explain the purpose of each 'R'.

Refinement:

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Reduction:

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Replacement:

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Explain why is it important that animals are properly kept, and stress is minimised?

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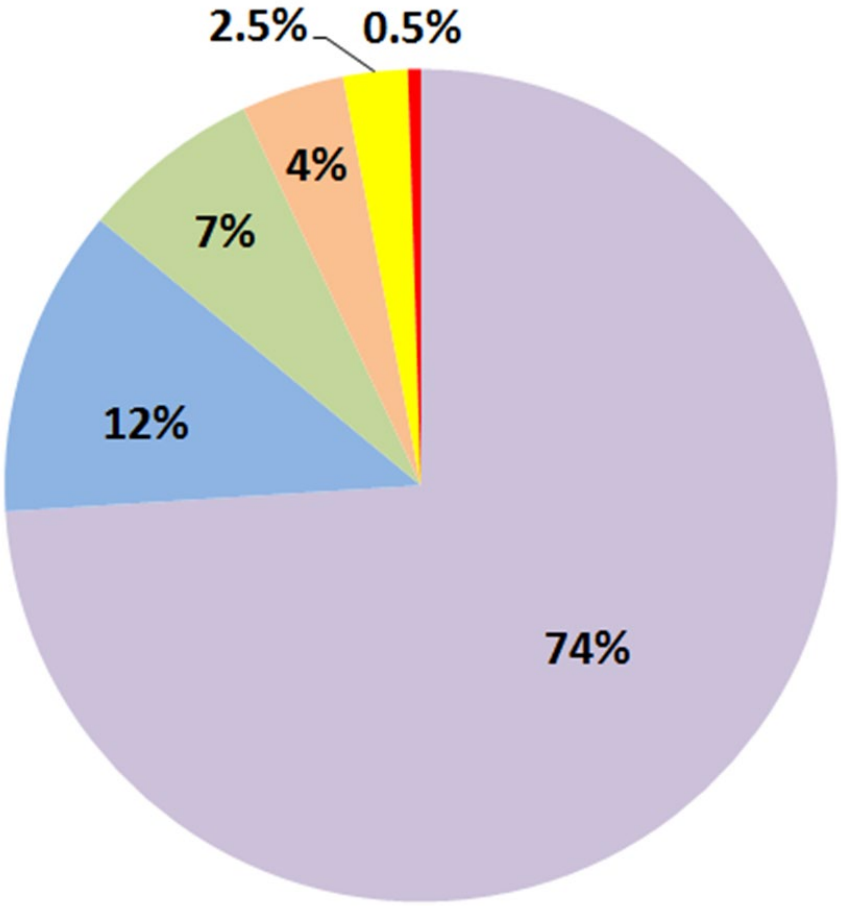
Activity 3:

Below is a pie chart that represents the different types of animals used in research.
Which percentage applies to which animal?



Animal	**Percentage**
Fish	
Rats	
Birds	
Mice	
Reptiles/amphibians	
Other mammals	

Tutorial 4 Notes:

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Homework:

Research and create an A4 poster on animal testing. The poster can be either in favour or against animal testing.

You may wish to pick a specific aspect of animal testing such as:

- The use of primates in animal research.
- Use of 'lower' organisms such as fish vs Use of 'higher' organisms such as mice.
- The effects on research if animal testing was made illegal.
- Alternatives to animal research.

Use your poster as a way of informing others of your opinion by showing the key facts you have discovered in your research.

Success criteria:

- Your poster must cover one aspect of animal research
- Your poster will include a title, images, and key information.
- Your poster will include suitable information that has been sourced – you should reference key facts. (See appendix -1)
- Your poster should be well presented and have accurate spelling, punctuation and grammar.

Tutorial 5 – How Do We Test Drugs on Humans?

What is the Purpose of Tutorial 5?

- To describe the purpose of clinical trials in humans.
- To identify the different phases of clinical trials.
- To describe some of the risks involved in clinical trials.

Activity 1:

Clinical trials are carried out in different phases. Any drug candidate that is deemed unsuccessful does not progress into the next phase of clinical trials. Each phase of a clinical trial aims to investigate different aspects of safety and efficacy.

Fill in the table below using the information provided by the teacher:

Phase	Number of volunteers	Purpose of trial
I		
II		
III		
IV		

Activity 2:

Thalidomide changed our relationship with new medicines forever.

It took five years for the connection between Thalidomide taken by pregnant women and the impact on their children to be made. Not only did Thalidomide change people's lives, but it also resulted in tighter drug testing and reporting of side effects. Before the Thalidomide scandal drugs could be approved for human consumption based on animal testing alone.

Explain how modern drug development aims to reduce another repeat of the Thalidomide disaster?

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Tutorial 5 Notes:

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Final assignment question:

In modern drug discovery, it can take up to 15 years after a drug is initially discovered before it is available for use by doctors for treating patients.

Describe the process of modern drug design and development to explain why it takes such a long time for a new medicine to become available for use.

Details of the assignment:

Write a 2000-word essay on how new medicines are developed. Make sure to discuss how medicines are designed, synthesised, and then tested to make sure they are safe and have the desired effect.

Some key points to include are:

- What makes medicines different from other types of drugs?

- Describe how scientists discover potential drug candidates.

- Outline the key stages in the development of drug candidates.

- Explain the importance of each stage of development.

The essay should be written in an appropriate scientific style and should include an introduction, discussion, and conclusion. All figures and tables must be appropriately labelled with captions. References should be used throughout.

In this assignment, show me that you **understand**:	Show me that you **are able to**:
- What the difference is between therapeutic, recreational, and illegal drugs. - What 'drug candidates' are and how they might be designed and synthesised. - The role of pre-clinical trials in drug development (*in vivo* ***vs*** *in vitro)*. - How and why animal clinical trials are carried out. - How and why human clinical trials are carried out.	- Explain scientific concepts using the correct language. - Draw upon reliable, scientific, material to support claims. - Describe and comment on the importance of current scientific practices.

Tutorial 6 – Feedback tutorial

What is the Purpose of Tutorial 6?

- To receive feedback on your final assignment
- To respond to the feedback from your Uni Pathways teacher
- To write targets for improvement on your final assignment

Final assignment feedback from your Uni Pathways Teacher

(Remember to look at the mark scheme to help you understand what you have done well so far, and how you can do even better in your final assignment)

Here are three things that my Uni Pathways Teacher thought I did well in my draft assignment
•   •   •

Here are three things that my Uni Pathways Teacher thinks that I could do to get a higher mark on my final assignment
•   •   •

Tasks from my Uni Pathways Teacher to do during the feedback tutorial to help me improve
•   •   •
My response:

Actions I will take to improve my final assignment after this tutorial…
•   •   •

Hand in date for my final assignment:	

Tutorial 7 – Final tutorial

What is the Purpose of Tutorial 7?

- To receive feedback and a grade on your final assignment.
- To reflect on the programme including what you enjoyed and what was challenging.
- To ask any questions you may have about university.

Final assignment feedback from my Uni Pathways Teacher

Final mark:	University style grade:
Feedback: Here are three things that my Uni Pathways teacher thought I did well in my final assignment • • •	

Here are three things that my Uni Pathways teacher thinks I should remember for when I am doing this kind of study in the future
• • •

University

What questions do you still have about University after taking part in Uni Pathways?
•   •   •

Reflecting on Uni Pathways

What did you most enjoy about Uni Pathways?
•   •   •

What did you find challenging about the programme?	How did you overcome these challenges?
• • •	• • •

Appendix 1 – Referencing correctly

When you get to university, you will need to include references in the assignments that you write, so we would like you to start getting into the habit of referencing in your Brilliant Club assignment. This is really important because it will help you to avoid plagiarism. Plagiarism is when you take someone else's work or ideas and pass them off as your own. Whether plagiarism is deliberate or accidental, the consequences can be severe. In order to avoid losing marks in your final assignment, or even failing, you must be careful to reference your sources correctly.

What is a reference?

A reference is just a note in your assignment which says if you have referred to or been influenced by another source such as a book, website or article. For example, if you use the internet to research a particular subject, and you want to include a specific piece of information from this website, you will need to reference it.

Why should I reference?

Referencing is important in your work for the following reasons:

- It gives credit to the authors of any sources you have referred to or been influenced by.
- It supports the arguments you make in your assignments.
- It demonstrates the variety of sources you have used.
- It helps to prevent you from losing marks or failing, due to plagiarism.

When should you use a reference?

You should use a reference when you:

- Quote directly from another source.
- Summarise or rephrase another piece of work.
- Include a specific statistic or fact from a source.

How do I reference?

There are a number of different ways of referencing, and these often vary depending on what subject you are studying. The most important to thing is to be consistent. This means that you need to stick to the same system throughout your whole assignment. Here is a basic system of referencing that you can use, which consists of the following two parts:

1. **A marker in your assignment**: After you have used a reference in your assignment (you have read something and included it in your work as a quote, or re-written it your own words) you should mark this is in your text with a number, e.g. [1]. The next time you use a reference you should use the next number, e.g. [2].
2. **Bibliography**: This is just a list of the references you have used in your assignment. In the bibliography, you list your references by the numbers you have used, and include as much information as you have about the reference. The list below gives what should be included for different sources.

    a. **Websites** – Author (if possible), the title of the web page, website address, [date you accessed it, in square brackets].

    E.g. Dan Snow, 'How did so many soldiers survive the trenches?', http://www.bbc.co.uk/guides/z3kgjxs#zg2dtfr [11 July 2014].

    b. **Books** – Author, date published, the title of the book (in italics), pages where the information came from.

    E.g. S. Dubner and S. Levitt, (2006) *Freakonomics*, 7-9.

    c. **Articles** – Author, 'title of the article' (with quotation marks), *where the article comes from* (newspaper, journal etc.), date of the article.

    E.g. Maev Kennedy, 'The lights to go out across the UK to mark First World War's centenary', Guardian, 10 July 2014.

Appendix 2 – Developing a novel drug

Published by the Wellcome Trust, the 'Big pictures' exploring issues around biology and medicine - 2009

Developing a novel drug

Drug development is a long and expensive process

A drug can be developed in a whole host of different ways. Constant improvement in technology has transformed drug design over the past few decades. Now, many laboratories in both universities and pharmaceutical companies make use of computers, robotics and artificial intelligence to aid in drug design. These techniques coupled with more traditional methods are becoming increasingly successful in designing novel drugs. One commonality between all the methods of drug design is that they are fraught with challenges. A pharmaceutical company may start with thousands of chemical compounds as potential drug candidates. Rigorous testing will whittle this down to a single chemical compound that can then be licensed to treat patients. Developing drugs is a risky and expensive business, but the potential profits are huge. The following step-by-step process provides a guide to how a compound in the laboratory becomes a disease-fighting drug. Option 1 explains the process of transforming initial research in a university lab (or biotechnology company) into a potential drug – about a quarter of drugs approved by the FDA between 1998 and 2007 began in this way. The remaining three-quarters began in pharmaceutical companies, as explained in option 2.

STEP 1 – OPTION 1: Origins in the research lab

In universities and research institutes all over the globe, many scientists dedicate their lives to understanding the molecular details of disease – how the disease works. By using animal models, usually mice, they are able to identify specific biochemical pathways that are altered by the disease. A small team of scientists will study a pathway and identify a potential therapeutic target, usually a protein. To effectively target this protein, they require a detailed 3D structure, often determined by a method known as crystallography, which records the pattern of X-ray scattering by atoms when a compound is exposed to a beam of X-rays. This field, known as structural biology, allows us to analyse the complex structure of the molecule and find areas that a drug could target. Their findings will be published in scientific literature. By using the detailed structure, scientists can use computational techniques to predict how a chemical compound might bind to the target protein. Computational techniques are cheaper than high-throughput screening – testing real interactions between large numbers of compounds and targets – but still, allow scientists to test a range of different compound structures. However, computational techniques are not without fault. The technology still lacks the ability to predict perfectly how a compound will bind. Chemical experiments called assays can confirm binding in vitro and structural biology can show how well a compound binds to the target. This initial drug structure is then ready to be fine-tuned into a final structure – but this requires money and resources that the scientists probably do not have. At this stage, the scientists may decide to set up a 'spin-out' company. To do this, the researchers would often have to leave their normal jobs to work in a commercial environment. They would then work solely on developing a drug to target the protein. They would also be required to seek investment from venture capitalists, investors who put money into high-risk projects, to fund their company. Alternatively, the scientists could remain at their jobs and team up with a small biotech firm. At this point, it is too early for pharmaceutical companies to be interested. The biotech firm will apply for 'seed' funding to provide the money required for the scientists to test their agents further. Whether they set up a spin-out company or team up with a biotech firm, the process of fine-tuning will be similar. They will use a combination of computational techniques, assays and structural biology to determine how the compound is binding. They will then change small aspects of the compound so it will act more efficiently on the target protein. At the end of all of this, they will have a final structure, but there is still a very small chance that this agent will make it to market. The biotech firm or spin-off company has gone as far as it can go. They require the monetary resources for expensive research and clinical trials that a pharmaceutical company can provide. They therefore often decide to enter a partnership with a large pharmaceutical company.

STEP 1 – OPTION 2: Origins in pharma

Pharmaceutical companies also employ large teams of scientists to research their own, similar to that of the work done in universities or research institutes. However, their work often focuses directly on potential therapeutic targets from the outset. This differs from research lab work, which might at first just aim to better understand a disease. Importantly, pharma has access to far more resources, allowing them to carry out much larger studies. They often use automated high-throughput screening (HTS) to identify initial potential compounds. This involves testing a vast number of different compounds' abilities to bind the target protein. Today's most advanced HTS technology platforms use fully articulated robot arms to carry out tens of thousands of tiny experiments and can cost upwards of $1 million (£0.8 million). Once candidate drug compounds have been identified, the company will carry out further tests to reduce this library to a single compound. Pharmaceutical companies are also beginning to use artificial intelligence, or machine learning, to aid drug discovery. This means they use powerful computer programs to make sense of large amounts of data. Being able to rapidly analyse data from multiple sources (including research papers and clinical trials) could give companies new ideas about the kinds of molecules they screen for certain conditions and help narrow down the search faster. Pharmaceutical company Pfizer is already using this method to look for potential cancer drugs.

STEP 2: Toxicity and animal testing

The pharmaceutical company can run many tests to find out how the agent might behave in the body, initially checking in animal studies for signs of toxicity and characterising further effects on the target. The company's scientists will assess how the agent is metabolised, how long it stays in the animal and where it goes. Often, compounds that seem to work very well in the lab, behave very differently when they are transferred to live animals. There may be problems associated with delivering the compound to the right tissues or in getting it to bind specifically to its molecular targets and only those targets. After more chemical refinement, the agent will finally be ready to be tested in people.

STEP 3: Trials and tribulations

Once the agent has passed its toxicity tests and animal models have confirmed that it should tackle the disease in people, phase I clinical trials can begin. A small number of usually healthy volunteers receive the drug in low doses. Volunteers could also be very ill patients who have not responded to other treatments. The volunteers are monitored carefully for any ill effects. If the drug proves to be safe at this stage, it can advance to phase II trials. Phase II trials involve a small group of patients – up to a few hundred. These trials ensure that the drug is safe for people with the disease to take and that it does have beneficial effects. Any drug that fails here will be an expensive loss. After phase II, around a third of drugs move on to phase III trials. Phase III trials test the drug in larger numbers of patients, potentially thousands, and confirm the beneficial effects. The greater the number of patients used in phase III, the more accurate the results of the study will be. Ideally, phase III trials involve comparing the drug's effects to a placebo or standard treatment and are double-blinded, meaning that neither the person administering the drug nor the person receiving it, know whether the drug or a placebo is being given.

STEP 4: Convince the regulator and then the doctors

Once a drug has progressed successfully through the first three stages of clinical testing, the company can apply for regulatory approval. Approval may take up to a year, or longer. All of the data collected during the research and clinical trials are submitted to the licensing body. In the UK, this is the Medicines and Healthcare Products Regulatory Agency, although most novel drugs currently come to market via a centralised EU process under the European Medicine Agency. In the US, it is the Food and Drug Administration. The licensing body may request more research in response to any concerns they might have – for example, if there is an indication of any potentially harmful side-effects – before issuing a license. If the drug

finally gains a license, the pharmaceutical company must then convince health providers that it is worth making available to their patients. Central to this process in the UK is the National Institute for Health and Clinical Excellence (NICE). They will decide whether the drug offers good value for money; without their seal of approval, the drug will never make it to patients. After NICE's approval, the pharmaceutical company can begin marketing the drug to doctors. Unlike in the US, pharma is not allowed to market directly to patients in the UK. Convincing doctors to prescribe the drug is the final step in the process. It may still take years for the drug to reach every patient. Clinical trials also continue post-approval and marketing as new drugs become available to more people. As in phase III testing, the gold standard is a randomised controlled trial (RCT), which compares the drug's safety and effectiveness in two groups of patients – one taking the drug and another taking a placebo or receiving standard treatment. In RCTs, patients are randomly assigned to one of these groups. Many different RCTs may be carried out over many years and in different types of patients and settings, to continue establishing safety and efficacy. Periodic reviews of collections of these trials may eventually bring to light issues that were not raised during the pre-approval process.

Appendix 3 – The Discovery of penicillin

Extract from "The discovery and development of penicillin 1928-1945" commemorative booklet produced by the National Historic Chemical Landmarks program of the American Chemical Society in 1999.

Alexander Fleming's Discovery of Penicillin

Penicillin heralded the dawn of the antibiotic age. Before its introduction, there was no effective treatment for infections such as pneumonia, gonorrhoea or rheumatic fever. Hospitals were full of people with blood poisoning contracted from a cut or a scratch, and doctors could do little for them but wait and hope.

Antibiotics are compounds produced by bacteria and fungi which are capable of killing, or inhibiting, competing microbial species. This phenomenon has long been known; it may explain why the ancient Egyptians had the practice of applying a poultice of moldy bread to infected wounds. But it was not until 1928 that penicillin, the first true antibiotic, was discovered by Alexander Fleming, Professor of Bacteriology at St. Mary's Hospital in London. Returning from holiday on September 3, 1928, Fleming began to sort through Petri dishes containing colonies of Staphylococcus, bacteria that cause boils, sore throats and abscesses. He noticed something unusual on one dish. It was dotted with colonies, save for one area where a blob of mold was growing. The zone immediately around the mold—later identified as a rare strain of Penicillium notatum—was clear, as if the mold had secreted something that inhibited bacterial growth.

Fleming found that his "mold juice" was capable of killing a wide range of harmful bacteria, such as streptococcus, meningococcus and the diphtheria bacillus. He then set his assistants, Stuart Craddock and Frederick Ridley, the difficult task of isolating pure penicillin from the mold juice. It proved to be very unstable, and they were only able to prepare solutions of crude material to work with. Fleming published his findings in the British Journal of Experimental Pathology in June 1929, with only a passing reference to penicillin's potential therapeutic benefits. At this stage, it looked as if its main application would be in isolating penicillin-insensitive bacteria from penicillin-sensitive bacteria in a mixed culture. This at least was of practical benefit to bacteriologists and kept interest in penicillin going. Others, including Harold Raistrick, Professor of Biochemistry at the London School of Hygiene and Tropical Medicine, tried to purify penicillin but failed.

Notes

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