

MSc in Drug Discovery and Pharma Management Course Information 2012/13

Part I:

1. The Department of Pharmaceutical & Biological Chemistry

The MSc in Drug Discovery and Pharma Management course is based in the Department of Pharmaceutical & Biological Chemistry.

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Academic Staff:

Professor Simon Gibbons	Head of Department, Prof in Phytochemistry
Professor Stephen Neidle	Professor of Chemical Biology, Director of Centre for Cancer Medicines
Professor Anne Stephenson	Professor of Molecular Neuroscience
Professor Steve Brocchini	Professor of Chemistry and Drug Delivery
Professor Klara Valko	Senior Investigator, GlaxoSmithKline

Professor Nigel Ratcliffe	ex-Vice-President, Regulatory Affairs, AstraZeneca
Dr Andy Wilderspin	Lecturer in Pharmaceutical Biochemistry
Dr Gary Parkinson	Lecturer in Structural Biology and Chemistry
Dr Steve Hilton	Lecturer in Chemistry
Dr Geoff Wells	Lecturer in Chemistry
Dr Min Yang	Lecturer in Mass Spectrometry
Dr Colin James	Molecular Modelling
Dr Sab Takhar	Clin Director Celgene, Visiting Lecturer
Dr Mike Brownleader	CEO Generon, UK, Visiting Lecturer

2. The MSc in Drug Discovery and Pharma Management Course

The MSc in Drug Discovery and Pharma Management is a 12 month full-time taught postgraduate course intended for graduates in science-based subjects who wish to pursue a career in the pharmaceutical or biotechnology industry with a management or business development role.

This course combines a broad overview of the drug discovery and development process with a deeper insight into the regulatory and commercial aspects of management in the pharmaceutical industry.

The model for drug discovery in the pharmaceutical industry is changing. “Me too” products, may no longer be commercially viable. Pricing of new products and market access is becoming more difficult. Today major companies are looking for more innovation from outside their own laboratories. AstraZeneca are publicly stating that they expect to buy 40% of their science externally in future. Merck and Pfizer say their growth will be from small product deals or acquisition of smaller enterprises. In this environment research scientists can be involved in evaluating the business potential of their science as well as generating the science itself. There will be real opportunities for business development and scientific enterprise.

This programme contains the science core of the MSc in Drug Discovery plus introductory and advanced level modules addressing Business Management. It is led by Dr Mike Munday, UCL School of Pharmacy and Dr Nigel Ratcliffe (visiting Professor and former Vice President Regulatory and Commercial Affairs Astrazeneca). The course provides a broad overview of the drug discovery and development process from drug target validation through the identification of lead compounds and their pre-clinical and clinical development into active drugs and medicines. The course covers marketing, licensing and regulatory affairs but specializes in management training and awareness and Strategic Partnering and Business Development skills.

3. Course Structure

The MSc course is designed to allow participants to gain a broad overview of the pipeline of drug discovery and development with a deeper insight into pharma management. This will bear particular reference to regulatory and commercial affairs in the pharmaceutical industry and the opportunities for business development .

The course outlines the molecular basis of disease and the identification and validation of drug targets. It investigates the various approaches to the identification of lead compounds and their development into active drug candidates. The course exposes students to modern platforms for drug discovery and methods of drug synthesis and includes lectures from industry-based scientists and visits to industrial and biotechnological research laboratories. Students gain hands-on experience of molecular modeling and computer-based drug design, and analytical and synthetic techniques. The approach of the pharmaceutical industry to pre-clinical development, clinical pharmacology, clinical trials, marketing, licensing and regulatory affairs form an integral part of the drug development process that is studied.

In the second semester students study two specialist modules in Pharma Management covering topics such as Research and Clinical Development, Intellectual property, Commercial Teams, Global Regulatory Affairs, Agencies, Hearings and Approvals, Risk Management, Post Approval Obligations, Commercialisation, Product Design and Launch for Market, Pharma Company Structure, Industrial Relations, Investor Relations, Strategic Partnering and Business Development, Due Diligence, Financial Analysis, Business Case, Communication Skills.

The course culminates in a business development project based on an aspect of science from drug discovery that will be supervised by academic scientists and business managers and can be carried out in the School of Pharmacy or as an extramural placement in industry.

The list of taught modules may change from year to year due to staff availability and every effort is made to inform students of any changes before the course starts. Some lectures are shared with final year students on the Master of Pharmacy degree.

First Semester

The first and second semesters comprise a taught core module.

Core module: The Process of Drug Discovery and Development (180 hrs contact)

This module is the core of the whole course following the process of drug discovery and development and runs throughout the first and second semesters. It introduces the basis of the pharmaceutical industry through examining previous successes and current methods of drug discovery. The core module includes:

Introduction to the molecular basis of disease, identification and validation of drug targets. (Dr M Munday)

The molecular basis of disease is considered with examples of infection, genetic and multifactorial clinical conditions and the mechanism of action of certain drugs in their therapy. There is a detailed revision of basic macromolecular structure and the types of cellular components that constitute drug targets. This section examines the identification of drug targets and the genomic approaches to the validation of drug targets.

Drug Discovery and Lead Identification (Dr M Munday; Prof S Neidle; Prof R Waigh; Dr G Wells)

The identification of drugs for human use has a long and fascinating history with its origins in witchcraft and magic through to the present time where techniques such as computer modeling, combinatorial synthesis and high-throughput screening are used. This section begins with a discussion of how ancient civilizations utilized a combination of witchcraft, magic and materials extracted from plants, animal and humans to attempt (usually unsuccessfully) to cure diseases. A number of natural products with genuine therapeutic activity such as salicin from willow bark (as an anti-inflammatory) and honey (as an antibacterial) were discovered in this period and will be described in more detail. Discussions will then move to a later period where chemical techniques, although in their infancy, were used to isolate and structurally elucidate well known natural products such as the major plant alkaloids. Discussion will then move to more modern times describing how modern drug leads are identified by a number of different techniques including combinations of molecular modeling, combinatorial libraries and high-throughput screening. The delivery of this module is supplemented by keynote lectures from academic and industrial experts with personal examples of drug discovery successes.

Advances in synthetic chemistry (Dr J Malkinson; Dr S Hilton)

Key themes of the application of modern synthetic methods in medicinal chemistry and drug discovery are covered in this section. Chemical-synthetic techniques that are utilized in the preparation of compounds for use in the chemical genetic approach will be discussed; importance will be given to the generation of novel natural product-like or -derived compound libraries. Topics include reaction mechanisms and asymmetric synthesis, combinatorial chemistry, pericyclic and multicomponent reactions, solid phase and microwave chemistry, and chemistry in flow.

High Throughput Screening of Compound and Natural product Libraries (Dr A Wilderspij; Dr P Groot-Kormelink, Novartis)

This section examines the types, molecular basis and technical procedures of biochemical and cell-based bioassays. Understanding the automation of the HTS process and the importance of bioinformatics and data processing in identification of lead compounds is an important component.

Molecular modeling and Structure Based Design (Dr M Zloh; Dr G Parkinson; Dr C James; Prof S Neidle)

This section is designed to introduce the student to the principles and practice of modern drug discovery. The course will provide an awareness of rational drug design, based on understanding the three-dimensional structures and physicochemical properties of drugs and receptors. There is considerable “hands on” experience of computational chemistry and computer-based molecular modeling. This section will cover modeling drug/receptor interactions with the emphasis on molecular mechanisms, molecular dynamics simulations and homology modeling. Other topics will be selected from: conformational sampling, macromolecular folding, structural bioinformatics, receptor-based and ligand-based design and docking methods, *in silico* screening of libraries, semi-empirical and *ab-initio* methods, QSAR methods, molecular diversity, design of combinatorial libraries of drug-like molecules, macromolecular and chemical databases

Physicochemical Properties of Drugs (Absorption, Distribution Metabolism) (Prof Klara Valko, GSK)

This section provides understanding of the physicochemical properties of molecules that can be used for compound selection at the early discovery stage. Students will study the traditional and newer high throughput methods for the determination of lipophilicity, solubility and pKa values and get an insight of the *in silico* calculations of these properties using software packages. Students will gain an understanding of how physicochemical properties influence cell permeability, oral absorption, protein binding, and blood/brain barrier distributions by discussion of various predictive models published in the literature.

Course content includes: Discussion and practical demonstrations of methods for lipophilicity determination (octanol/water partition, chromatographic hydrophobicity index, micellar electrokinetic chromatography). Discussion and demonstration of methods for solubility determinations and their automation. Practical determinations of pKa values. Commercially available instruments with various levels of automation.

The Abraham solvation model for describing lipophilicity as a composite parameter, comparison of various organic solvent/water partitions. Measurements and calculation of the Abraham molecular descriptors. The effect of ionisation on the lipophilicity and solubility of the molecules at various pHs. Membrane partitioning, immobilised artificial membrane chromatography, parallel artificial membrane partition, liposome partitioning. Calculation of lipophilicity, solubility and pKa from the structure, familiarisation with commercial software packages (clogP, ACDlogP, pKalc, Pallas logP/D, Absolv). Various models of passive oral absorption (Abraham model, logD/cMR model, polar surface area, etc.). Design of drugs for oral absorption. Various methods for measuring protein binding and its significance to the pharmaco-kinetic profile Modeling blood/brain barrier distribution based on physicochemical properties, predicting CNS penetration.

Preclinical Development (*Dr G Meneses-Lorente, Roche; Dr M Munday, Dr R Smyth, Dr J Turton*)

This section covers phase 1 and phase 2 drug metabolism and factors that affect these processes. This includes chemical modification and the use of prodrugs to protect from metabolism. The industrial approach to Clinical Pharmacology is covered by Dr G Meneses-Lorente (Roche). The use of preclinical toxicology studies which are necessary before the drug can be administered to humans will be discussed in detail.

Clinical Development (*Dr R Williams, CRUK; Dr S Takhar, Celgene; Dr R Gomez, Oxford; Dr K Sheikh*)

The choice, preparation for and execution of the four phases of clinical trials are investigated. External experts from Celgene (Dr S Takhar), CRUK (Dr R Williams) plus Quintiles and the NHS discuss a variety of issues and expertise.

Regulatory Affairs, Commercial Affairs and Intellectual Property (*Prof Nigel Ratcliffe, ex-Vice President Regulatory Affairs, AstraZeneca; Mr P Bhartiya, MHRA*)

Discovering lead compounds and then developing them towards a marketable product are only the first two components of a very complex and expensive process. Once a lead compound has been suitably developed it then has to be tested extensively in animals before going into the first human clinical trials. If it successfully completes these trials, then the company has to apply for a license to market the product from the appropriate Government agency e.g. FDA in the USA, MHRA (Medicines and Healthcare products Regulatory Agency, formally the MCA) in the UK. Before granting a license, these agencies will require extensive evidence that the product is efficacious and safe i.e. has a positive risk/benefit ratio. Even after a product license (e.g. a Marketing Authorization in the UK) is granted, the Government agencies of all countries in the developed world operate a Post Marketing Surveillance system supported by many different types of health workers, including doctors, pharmacists and nurses who report any adverse drug effects. If it becomes evident that in the larger general population the risk/benefit ratio is larger than anticipated, then the MA can be withdrawn.

It is crucial that Intellectual Property (known as IP) surrounding novel drug products are protected by processes such as filing patents and registering trade marks. Once protection is in place, a company that may have spent many millions discovering and developing a product can then freely market it for approximately 20 years in the countries in which it is protected without fear of other manufacturers marketing a similar or generic product. Once patent protection has lapsed, then other companies are free to market generic versions of the products. This section will describe in detail all aspects of the IP protection process. It will discuss the recent trends for large pharmaceutical companies to merge into large international conglomerates, and for the formation of numerous small start-up biotechnology companies often based around academic programmes of research. These changes have transformed the pharmaceutical industry in the last 10 years with a trend towards new lead molecules being discovered, predominantly by smaller companies which then license their IP to

the larger merged pharmaceutical companies. Many of the latter focus more on lead development, clinical trials and marketing than lead discovery.

In the first semester the Core module is supported by two smaller modules

Module 1: Modern Aspects of Drug Discovery

Drug discovery through the molecular sciences involves a combination of modern methods of lead identification, activity optimization, synthesis and/or isolation, and characterization. A number of aspects of small molecules as drugs will be discussed in this module. The development of antibiotics are described by Dr Paul Stapleton. The discovery of insulin and the use of recombinant proteins as medicines are explored (Dr Munday). The story of the discovery and development of beta blockers is described (Dr Munday). The importance of synthetic chemistry to modern drug discovery is explained (Dr Stephen Hilton) and the use of inhibitors of protein-protein interactions as potential drugs is explored (Dr Geoff Wells). The development of drug discovery from natural products to strategic computer-based drug design is illustrated with examples of drugs acting on enzymes (Dr Wilderspin). Drugs acting on membrane proteins, in particular, the relevance of membrane composition, structure and properties will be addressed along with discussions on the role of lipid bilayers and protein folding (Dr Zloh).

Module 2: Pharmaceutical Analysis

A basic knowledge of the analytical techniques required to detect and identify compounds and to determine their physicochemical properties is essential. Furthermore, such analysis is critical in subsequent quality control of drugs and medicines. In this module students will study the theoretical basis and practical use of a wide range of techniques, including ultraviolet, visible and infra-red spectroscopy and x-ray crystallography and the development of spectroscopic techniques in trace metal analysis. The principles of HPLC and its use and importance in the elucidation of drug properties are taught (Prof Valko, GSK). The use and importance of NMR in molecule identification and modelling is introduced (Dr Zloh) and the applications of mass spectroscopy and an introduction to proteomics is provided (Dr Yang). The basis of electrophoretic and immunological techniques that are essential in drug target validation concludes this module (Prof Stephenson).

First Semester Practical Classes:

- Six 3hr hands-on computer-based molecular modeling practicals.
- 3hr practical "uv-vis and infra-red spectroscopy". Uses a visible-spectrophotometric assay to examine enzyme inhibition by an unknown drug and infra-red-spectroscopy to identify the drug.
- 3hr practical "HPLC" uses reverse phase HPLC to determine purity of a drug.
- 3hr tutorial based introduction to NMR and mass spectrometry equipment.
- 4hr practical "SDS-polyacrylamide gel electrophoresis" examines subunit structure of a protein and its susceptibility to proteolytic degradation.

- 4hr practical on “extraction and isolation of natural products”.
- 4hr medicinal chemistry practical in organic synthesis and characterization of product
- 3hr practical to assay enzyme activity and examine enzyme inhibition by an unknown drug.

Second Semester

In the second semester the main core module continues:

Core module: The Process of Drug Discovery and Development (180 hrs contact)

Students also study two core modules in Pharma Management

Pharma Management Module 1

(Prof Nigel Ratcliffe, ex-VP Regulatory and Commercial Affairs, AstraZeneca; Miss Emma Keogh CIMA Accountant; Dr Phil Holt Executive Clinical Director AstraZeneca)

This module will cover the following key areas:

- (i) The team approach to Research and Clinical Development. The module will discuss the important input from:
 - Clinical Development
 - Intellectual property.
 - Commercial Teams.
- (ii) A key part of the module will focus on Global Regulatory Affairs and thus incorporate the different steps involved:
 - Regulatory Objectives
 - Regulatory Agencies.
 - Global Regulatory Package.
 - Global Process
 - Hearings and approvals
 - What does an approval provide
 - Risk Management and post approval obligations.
- (iii) The final part of the module will introduce the student to the considerations to be taken into account when commercialising a product. Discussions will take place concerning:
 - What is the market?
 - How do you design a product for a market?
 - How do you launch your product?

Pharma Management Module 2

(Prof Nigel Ratcliffe, ex-VP Regulatory and Commercial Affairs, AstraZeneca; Miss Emma Keogh CIMA Accountant; Dr Phil Holt Executive Clinical Director AstraZeneca)

This module will cover the following key areas:

(i) How is a Pharmaceutical Company structured

What are the functions within the company, what is the governance and obligations?

What is the current Pharmaceutical environment? How is it changing?

Industrial relations

Investor relations.

Strategic Partnering and Business development. How is it run?

Searching for products

Initial evaluation

Due Diligence. The teams involved

Financial analysis

Introduction to all parameters studies. PYS, IRR eIRR NPV eNPV ROI etc.

The Business case.

Compilation and delivery of the Business case.

Media Training

Communication Skills.

Disclosure Committees

(ii) Product and Science Due Diligence.

Where DD fits in the process.

What the initial assessments will have told you and what the difference is here between early evaluation and Due Diligence.

What the team looks like.

What e rooms are, what paper rooms are like.

How a team is formed, who sits on the team and why?

Where a bench scientist may sit, what they will be doing.

What is the meeting like, who does what?

What are you looking for, what interactions do you have with their scientists.

Who rights the report, who takes notes? What's the legal standing of the reports? What do you do with the report?

The kind of issues you find, what are the problems? What to look for.

What to consider as an employee in Discovery? One day someone may undertake DD on your work.

(iii) Clinical Development

Study types

Phase 1 2 and 3.

The requirements pre tox for commencement of each phase.

Multi disciplinary teams. The role the scientist may play in metabolite

identification, sample analysis etc.
Centre selection.
Advisory board.
Safety Board,
Regulatory clearance
Ethics boards.
Use of contract organizations.
Data interpretation, audits.

(iv) Introduction to Financial Evaluation of Science and Product Evaluation.

The Financial Director in a Strategic Partnering and Business Development Team, what role do they play?

A financial business case. What do you look for, what parameters do you study, what are the terms and what do they mean.

What information do you need for a business case?

Who do you need to influence?

What measures would make a business case approvable, i.e. what are the acceptable limits for a pre clinical, phase 1, phase 2 opportunity etc.?

Venture capital, what does this mean? How does it work?

Basic Financial parameters.

4. Coursework

Coursework from selected individual topic areas supports and supplements the taught component of the MSc in Drug Discovery. These will be described by the member of staff responsible, and the format, length, outline of content and context expected for written material and the deadline for submission will be carefully explained. The different types of coursework tasks that are likely to be set include:

- Problem solving and calculations relating to pharmaceutical analysis
- Short reports or summaries and/or oral presentations of topics of interest or of data and conclusions from a published manuscript
- Practical write-ups
- Molecular modeling portfolio

In the first semester, there are two major pieces of coursework:

Case Study

Students are given specific topics to research and retrieve information each week for 3 weeks. Students are expected to prepare notes and collect references. In week 4, students write a report using data given to them about a potential new statin. This is a 3 hour "open book" session with published material available and

freedom to visit the library. Students hand in their report for assessment at the end of the 3 hours.

Molecular modelling portfolio and poster presentation on drug-target interactions

Students are provided with a 3 dimensional structure of a protein complexed with a drug. Each student has to analyse their own structure using the molecular graphics and modelling tools that are demonstrated during hands on sessions. Students have to produce a file with molecular graphic images to demonstrate their ability to visualize protein-ligand complexes, analyse interactions between a ligand and protein, and build and optimize small molecules.

Students with the same allocated protein in the molecular modelling exercise will then form a group and together produce a poster presentation containing important protein-drug interactions. The poster must demonstrate background knowledge about the selected protein as a drug target. The use of information concerning interactions between that protein and drugs in different complexes is required to provide understanding of important intermolecular interactions for that particular target.

In the second semester, there are two major pieces of work:

Analysis of Clinical Data Trial

Students are provided with 8 figures and tables taken from different clinical trials of a drug (eg Gleevec). Methodology is included but no interpretation of the data. Students have to interpret the data and draw conclusions in a report of approximately 2,000-3,000 words.

Critical Analysis of Pharma Management Report

Students are provided with a published report relating to some aspect of regulatory, commercial or business affairs within the context of drug discovery and development in the pharma industry. A critical review of the research methodology applied, the data and its interpretation, and the contribution of this report to a successful outcome or added value in the management process is required in a report of 2000-3000 words.

5. Research & Business Development Project

A major component of the MSc course is the business development project. Projects are assigned in February and are supervised by an academic member of staff in the Department of Pharmaceutical & Biological Chemistry and a business/management advisor. Projects are unique and will take an aspect of science relevant to drug discovery and develop a business case for getting this science to market. For example

it could be a case describing how to bring a novel molecule to market as a therapeutic agent, or it could be the strategy required to develop and market a diagnostic test. This work is undertaken between May and September. Students are expected to develop their own ideas and strategies in discussion with their supervisors and complete a comprehensive literature review to supplement their work. Business plans are written up and submitted as a dissertation and will be presented in an oral presentation to the class and a judging panel of scientists and managers at the end of the year.

6. Visit to a Leading Pharmaceutical Company

Students visit a leading research laboratory. This is usually an all-day visit to a company such as GlaxoSmithKline, where students look at computer-based molecular modeling, how physico-chemical properties are determined, the robotic compound library, high through put screening, and the chemistry and biology labs. The visit is supplemented by the provision of material and instruction, as well as lectures, to assist understanding of drug discovery and development. The discovery process of a drug will be worked through in detail.

Students also get to attend a one-day external research conference in an aspect of drug discovery during the course.

7. Assessment

There are three components of assessment:

- i. Semester I Module: continuous assessment by coursework assignments and one 3 hour written examination in February.
- ii. Semester II Module: continuous assessment by coursework assignments and one 2 hour open book written examination, and two 1.5hr written examinations in April.
- iii. Written research project report and oral presentation in early September.

The pass mark is 50% in all assessments, with an overall mark of 50% required for the award of the MSc. The weighting for each element of assessment is set out in the course regulations and marking scheme, which is given to students at the start of the course. Students who achieve an overall mark of 60-69% (and at least 65% in their project) will be awarded the MSc with merit, students who achieve an overall mark of 70% or higher are awarded the MSc with distinction.

Students who do not pass an assessment at the first attempt may, at the discretion of examiners, be referred and allowed to re-take the assessment. The maximum mark

awarded on successful re-assessment is 50%. The course regulations and marking scheme set out the specific details.

A final oral examination (viva) takes place in September. Only selected students are called to viva with the external examiner.

Provisional Calendar for 2012/13

Induction week	24-28 September 2012
Term 1	1 October to 7 December 2012 <i>Christmas holiday</i>
Term 2	7 January to 15 March 2013 <i>Exams 28 January to 1 February*</i> <i>Mid-term break 4-8 February</i> <i>Easter holiday (Easter on 29 March)</i>
Term 3	15 April to 30 September 2013** <i>Bank holidays on 6 & 27 May</i> <i>Exams: end April / early May*</i>
Graduation	to be confirmed

* To be confirmed by the Course Director.

** Please note that the end of Term 3 varies for different postgraduate courses.