
Faculty of Medicine

School of Medical Sciences

DEPARTMENT OF PHARMACOLOGY

# PHAR 3101
# Drug Discovery, Design and Development

## COURSE OUTLINE

SESSION 2, 2017

CRICOS Provider Code: 00098G

## CONTENTS



Please read this outline in conjunction with the following pages on the School of Medical Sciences website:

- Advice for Students
- Learning Resources

(or see "STUDENTS" tab at medicalsciences.med.unsw.edu.au )

# PHAR3101 Course Information

Drug Discovery, Design and Development (PHAR3101) is a 3rd year Science course worth six units of credit (6 UOC). The course is usually undertaken as part of a major in Pharmacology for the Bachelor of Science (Adv.) or Bachelor of Medical Sciences or as part of the Bachelor of Medicinal Chemistry. The course builds on the knowledge you have gained in Pharmacology (PHAR2011, PHAR3102 and/or PHAR3251).

## OBJECTIVES OF THE COURSE

This course will explore the process of drug development, from target identification to final drug registration. It will present drug development as a process involving target selection, hit discovery using computer-based methods and combinatorial chemistry/high-throughput screening. Lead identification and optimisation via the use of structure activity series and computational methods will be covered. Safety evaluation, bioavailability, clinical trials, and the essentials of intellectual property, regulatory affairs and commercialisation will also be discussed. Along the way, you will learn about screening assays, computer-aided drug design, and toxicology as applied to the development of new medicines.

## COURSE CO-ORDINATOR and LECTURERS:

Course Coordinator:

Dr. Angela Finch

a.finch@unsw.edu.au

Wallace Wurth Building, level 3E, ph: 9385 1325

Co-Coordinator:

Dr Natasha Kumar

natasha.kumar@unsw.edu.au

Wallace Wurth Building, level 3E, ph: 9385 1713

Students wishing to see the course coordinators should make an appointment via email as our offices are not readily accessible. We will organize to meet you in a convenient location elsewhere in the building.

Lecturers in this course:

| | |
|---|---|
| Dr Trudie Binder | w.binder@unsw.edu.au |
| Dr Orin Chisholm | o.chisholm@unsw.edu.au |
| Ms Teresa Domagala | Teresa.Domagala@tevapharm.com |
| Prof Peter Gunning | p.gunning@unsw.edu.au |
| Dr Greg Smith | g.smith@unsw.edu.au |
| Dr Alastair Stewart | a.stewart@victorchang.edu.au |
| A/Prof Laurence Wakelin | l.wakelin@unsw.edu.au |

## COURSE STRUCTURE and TEACHING STRATEGIES

Learning activities occur on the following days and times:

- Lectures: Wednesday 10-11am and 2-3pm; weeks 1-12
- Tutorials: Wednesday 3-4 pm or 4-5 pm; weeks 2-13
- Practicals: Tuesday 2-5 pm; weeks 1-12

Students are expected to attend all scheduled activities for their full duration (2 hours of lectures per week and 4 hours of practical and tutorial sessions per week. Students are reminded that UNSW recommends that a 6 units-of-credit course should involve about 125-150 hours of study and learning activities. The formal learning activities are approximately 70 hours throughout the semester and students are expected (and strongly recommended) to do at least the same number of hours of additional study.

Lectures will provide you with the concepts and theory essential for understanding the processes involved in drug development. To assist in the development of research and analytical skills practical classes and tutorials will be held. These classes and tutorials allow students to engage in a more interactive form of learning than is possible in the lectures. The skills you will learn in practical classes are relevant to your professional development.

## APPROACH TO LEARNING AND TEACHING

The learning and teaching philosophy underpinning this course is centred on student learning and aims to create an environment which interests and challenges students. The teaching is designed to be relevant and engaging in order to prepare students for future careers.

Although the primary source of information for this course is the material covered in lectures, tutorials, and practical classes, effective learning can be enhanced through self-directed use of other resources such as textbooks and Web based sources. Your practical classes will be directly related to the lectures and it is essential and required to prepare for practical classes before attendance *via* the pre-lab modules. It is up to you to ensure you perform well in each part of the course: preparing for classes; completing assignments; studying for exams and seeking assistance to clarify your understanding.

## TEXTBOOK AND READING LIST

Recommended Primary Texts:

- Drug Discovery and Development - Technology in Transition. Hill & Rang. Elsevier Ltd 2nd edition 2013.
- Pharmacology in Drug Discovery: understanding drug response T. P. Kenakin. Elsevier, 2nd Edition 2012.

These textbooks will be available at the UNSW bookshop. They are also available in print and online formats from the library.

**Other Resources:**

The following electronic journals are accessible *via* the UNSW library.

- Nature Reviews: Drug Discovery.
- Drug discovery today.
- Science online special “Drug discovery” www.sciencemag.org/sciext/drugdisc/
- Pharmacology & Pharmaceutical Medicine Study guide http://subjectguides.library.unsw.edu.au/medicine/pharmacology

Links to additional sources to supplement the material covered in the lectures will be placed on the lecture pages on Moodle.

## STUDENT LEARNING OUTCOMES

PHAR3101 will develop those attributes that the Faculty of Science has identified as important for a Science Graduate to attain and the Learning Objectives of the Pharmacology Major.

A. Research, inquiry and analytical thinking abilities.
B. Capability and motivation for intellectual development.
C. Ethical, Social and Professional Understanding.
D. Communication.
E. Teamwork, collaborative and management skills.
F. Information literacy.

Pharmacology Major Learning Outcomes

1. Demonstrate an understanding of how drugs/therapeutics are developed, work and are used safely.
2. Critically analyse, interpret and effectively communicate pharmacology data and literature.
3. Design and/or execute experiments or other activities to address pharmacological scenarios.

On completion of this course students should be able to:

- demonstrate an understanding of the steps involved in drug development from bench to bedside.
- apply knowledge of the drug development process, and identify challenges and benefits of different approaches to address novel scenarios.
- critically analyse scientific literature and experimental data and communicate their findings.
- show an understanding of teamwork and the contributions of different discipline areas to drug development

See also: UNSW Graduate Outcomes  Science Graduate Attributes

## ASSESSMENT PROCEDURES

- Progress exam (45 min duration): **10 %**
- Research Manuscript **20 %**
- Therapeutic product development history **15 %**
- End of session examination (2 hours duration) **55 %**
- Formative assessment

The *practicals and tutorials* are provided to support lecture material and practise analytical skills. The practical classes and tutorials help you to develop graduate attributes A, C, D & E.

You will submit a written report covering three of the practical sessions. The report should be in the form of a scientific communication comprising aims, results and discussion (see below for instructions). Students will also work in teams to research the drug discovery process of a given drug. They will submit a timeline and a written report on their findings. These assessment tasks will allow you to develop your research, information literacy, communication and time management skills, as well as allowing you to demonstrate your ability to work in a team and collaborate successfully (Graduate attributes A, D, E &F). The marking criteria and instructions are provided below.

A penalty will apply for late submissions of assessment tasks (10% per day).

The *progress examination* will be held during the 10 am lecture session in week 6, on the 30th of August. This exam will give you feedback on how you are succeeding in the course. The *progress examination* and *end of session examination* will test not only your knowledge of the process of drug design and development but also your ability to apply the knowledge you have acquired from multiple lectures, practicals and tutorials to drug development scenarios. The examination will be in the format of short and long answer questions. The questions will be based on the material covered in the lectures, practical classes and tutorials. Material covered prior to the progress exam may be examined again in the final exam. The examinations will address graduate attributes A and B. The end of session examination will be held during the official examination period.

The goal of *formative assessment* is to provide ongoing feedback that you can use to improve your learning. Formative assessment tasks help students identify their strengths and weaknesses and therefore the areas they should focus on. The formative assessment will take the form of tutorial questions. Tutorial questions will be posted on Moodle a week before scheduled tutorial sessions.

## COURSE EVALUATION AND DEVELOPMENT

Each year feedback is sought from students about the courses offered in the Department of Pharmacology and continual improvements are made based on this feedback. The UNSW myExperience survey is the way in which student feedback is evaluated and significant changes to the course will be communicated to subsequent cohorts of students. Also, a staff-student liaison group will be set up and students will be invited to become class representatives to seek feedback from their colleagues and meet with academic staff to discuss any issues that arise. Based on feedback given in these meetings changes will be implemented during the course and for future years.

We appreciate student feedback because we are always looking for ways to improve your learning experience in this course. Below is a summary of the feedback from the previous student cohort in this course and our response to how we improved this year's course delivery.

*Previous students told us that:*

They liked the structure and content of the course and that all the components were integrated. Especially that the course covers the Drug Discovery, Design and Development process from start to end. They really enjoyed and saw value in the practical labs and liked that the pre-labs helped them to prepare for the practical classes. They also liked all the assessment tasks especially the research manuscript based on a series of labs.

When asked what could be improved in the course the most frequent responses (5/20 comments) were to reduce the number of computer practicals and space out the assessment tasks (4/20). The other suggestions included increasing the word count on research manuscript, increase the weighting of each assignment, reduced focus on chemistry and provide more help with the assignments.

*We have responded to this feedback by:*

Reducing the number of computer based practicals and totally revising the remaining computer practicals to make them easier to understand and better integrated with the course material. The course content has been revised to place less emphasis on the medicinal chemistry phases of the drug development process. The weighting of the research manuscript (now 20%) and the therapeutic product development history (now 15%) has been increased. The word count for the research manuscript has been increased and a learning activity developed that provides examples and guidance on how to complete these assessment tasks has been introduced. Furthermore, the assessment tasks are more evenly spread across the semester. The weighting of the final exam has been reduced to 55%.

## GENERAL INFORMATION

The Department of Pharmacology is part of the School of Medical Sciences and is within the Faculty of Medicine. It is located in the Wallace Wurth building. General inquiries can be made at the BABS.SOMS.BEES (B.S.B.) Student Office, located on the Ground Floor Room G27, of the Biosciences Building. Office hours are 9.00 am - 5:00pm.

***Professor Margaret Morris*** is Head of Department and appointments to meet with her may be made via email (m.morris@unsw.edu.au).

***There is an honours program conducted by the School.*** The Honours program is coordinated by Dr Greg Smith (g.smith@unsw.edu.au), Ph: 9385 8075. Any students considering an Honours year should discuss the requirements with the coordinator.

Honours Administrator: Vicky Sawatt (v.sawatt@unsw.edu.au) Ph:9385 8195.

***Postgraduate degrees***

The Department of Pharmacology offers students the opportunity to enter the following graduate programs:

***Course Work Masters:*** Masters in Pharmaceutical Medicine. For more information contact Dr Orin Chisholm (o.chisholm@unsw.edu.au )

***Research Masters:*** In Pharmacology. Contact the post-graduate co-ordinators A/Prof Pascal Carrive (p.carrive@unsw.edu.au) and Dr Nicole Jones (n.jones@unsw.edu.au)

***Doctorate*** (***Ph.D)***: In Pharmacology. Contact the post-graduate co-ordinators A/Prof Pascal Carrive (p.carrive@unsw.edu.au) and Dr Nicole Jones (n.jones@unsw.edu.au).

### Enrolment and administrative help

The Student Administration Officers are available to help with problems with enrolment and scheduling, and should be the first point of contact for administrative problems. They can be found in the BSB Student Office, Room G27, Ground floor of the BioSciences Building. ph:9385 2464,

Email: SOMSenquiries@unsw.edu.au

### Attendance Requirements

For details on the Policy on Class Attendance and Absence see Advice for Students and the Policy on Class Attendance and Absence.

Attendance at practical classes is compulsory, and must be recorded in the class roll at the start of each class. Arrival more than 15 minutes after the start of the class will be recorded as non-attendance. It is your responsibility to ensure that the demonstrator records your attendance and no discussions will be entered into after the completion of the class. Satisfactory completion of the work set for each class is essential. It should be noted that non-attendance for other than documented medical or other serious reasons, or unsatisfactory performance, for more than 1 practical class during the session may result in an additional practical assessment exam or ineligibility to pass the course. Students who miss practical classes due to illness or for other reasons must submit a copy of medical certificates or other documentation to the course coordinator.

### Practical Classes

The practical class is an opportunity for students to develop graduate attribute C by behaving in an ethical, socially responsible and professional manner within the practical class.

Students must take due care with biological and hazardous material and make sure all

equipment is left clean and functional. In the interests of safety, special attention should be paid to any precautionary measures recommended in the notes. If any accidents or incidents occur they should be reported immediately to the demonstrator in charge of the class who will record the incident and recommend what further action is required.

For more details see Advice for Students-Practical Classes

## Special Consideration

You can apply for special consideration when illness or other circumstances beyond your control interfere with your assessment performance. Except in unusual circumstances, the duration of circumstances impacting academic work must be more than 3 consecutive days, or a total of 5 days within the teaching period.

You must make formal application for Special Consideration as soon as practicable after the problem occurs and within 3 working days of the assessment to which it refers.

**The application for all special consideration regardless of the percentage of the final grade it contributes must be made through Online Services in myUNSW** (My Student Profile tab > My Student Services > Online Services > Special Consideration).

Please see UNSW-Special Consideration and Student Advice-Special Consideration

If you unavoidably miss the progress exam in PHAR3101, you must lodge an application with UNSW Student Central for special consideration. If your request for consideration is granted an alternative assessment will be organised which may take the form of a supplementary exam or increased weighting of the final exam.

**The supplementary exams for the School of Medical Sciences in Semester 2, 2017 will be held on the 4th – 8th December 2017.**

## Student Support Services

Details of the available student support services can be found at Student Advice-Student support services.

## Appeal Procedures

Details can be found at Student-Advice-Reviews and Appeals

## Academic Integrity and Plagiarism

The School of Medical Sciences will not tolerate plagiarism in submitted written work. The University regards this as academic misconduct and imposes severe penalties. Evidence of plagiarism in submitted assignments, etc. will be thoroughly investigated and may be penalised by the award of a score of zero for the assessable work. Flagrant plagiarism will be directly referred to the Director of Integrity for disciplinary action under UNSW rules.

The UNSW Student Code outlines the standard of conduct expected of students with respect to their academic integrity and plagiarism.

More details of what constitutes plagiarism can be found here

# Drug Discovery, Design and Development

# LECTURE and PRACTICAL OUTLINES

The course is divided into 4 main themes covering the drug development process from bench to bedside.

1. Target Selection & Validation
2. Lead Identification & Optimisation
3. Pre-Clinical & Clinical Development
4. Registration & Commercialisation

## 1. Target Selection & Validation

Drug Discovery & Development: Choosing the project

This lecture will present the process of drug discovery and development, outlining the journey from test tube to patient treatment. It will introduce terminology used in drug discovery and development programs and discuss the role of multidiscipline teams in this lengthy, expensive, and complicated process. It will explore the factors that are considered when making the initial decision of whether or not to embark on a new drug discovery project.

Novel Target Identification and Validation

In this lecture, the role of genomics and bioinformatics in target selection will be explored. The use of genetic approaches to identify target candidates, genomics and proteomics will be covered. Also covered will be the role of bioinformatics in the analysis of nucleic acid sequence, protein sequence and structure, expression databases and functional pathway data contained in databases.

Target Validation and Drug Validation Practicals

Drug discovery teams (groups of 2-3 students) will validate a potential drug target, tropomyosin Tm5NM1, for the treatment of cancer. This novel target is suggested to control the proliferation of cancer cells. Having validated the target drug validation for Tm5NM1 will be carried out to verify specificity and desired impact on cell function.

*1. Target Validation*
Aims:

- To investigate changes in the actin cytoskeleton when the expression levels of Tm5NM1 is knocked down using small interfering RNA (siRNA).
- To investigate the impact of Tm5NM1 knockdown on tumour cell growth using a clonogenic colony forming assay.

*2. Drug Validation*
Aims:

- To investigate changes in the actin cytoskeleton when cells are incubated with the anti-tropomyosin compound TR100
- To investigate the impact of the anti-tropomyosin compound TR100 on tumour cell growth and determine the effective concentration ($EC_{50}$) using cell viability assays.

DNA as a Drug Target

DNA, messenger RNA, and ribosomal RNA are important molecular targets for cancer, viral, and microbial chemotherapy. Drugs that bind to these targets inhibit DNA replication, the transcription of mRNA, and its translation into proteins. In this lecture we will focus on how structure-based approaches have been applied to the rational design of DNA groove binding agents that recognise specific nucleotide sequences, and how this provides the opportunity for the development of gene-specific inhibitors of transcription – a holy grail of many molecular

pharmacologists.

Gene Modification Techniques in Drug Discovery

In the “Targets: DNA” lecture we focussed on DNA-binding agents that specifically inhibit the transcription of designated genes, here, in the “Targets: RNA” lecture we will consider the development of agents that selectively block mRNA so as to inhibit gene expression at the level of translation. We will discuss three different approaches: (1) the development of anti-sense oligonucleotides, (2) the design of ribozymes that selectively cleave designated mRNAs, and (3) the use of small inhibitory RNAs, known as siRNAs, in post-transcriptional gene silencing.

Target Selection

This lecture will discuss the key issues in target selection and discuss the rationale for decision making. We will explore the advantages and disadvantages of different proteins/nucleic acids as drug targets. The qualities that make a good drug target will be covered including: contribution to a biological pathway involved in the pathophysiology of a disease, functional and structural information about the target and that the target is “druggable” will be covered.

## 2. Lead Identification & Optimisation

Biological Assays: Hit Identification

This lecture will examine the types of assays that can be used to screen for hits as well as test compounds during lead optimization. We will compare different assay formats, such as biochemical verses cell based, homogenous verse heterogeneous, and target verses phenotypic assays. The advantages and disadvantages of each assay type will be explored.

High Throughput Screening

The introduction of new technologies, such as high throughput screening (HTS), which can experimentally test hundreds of thousands of compounds a day, has resulted in a more rapid identification of promising drug candidates and reduced drug development costs. This lecture covers assay development and the qualities needed in a screening assay. The role of high throughput screening and the advantages and challenges it brings to the drug discovery process will be discussed.

Hit Identification and Lead Modification Practicals:

Drug discovery teams (groups of 3-4 students) will test a series of structurally related compounds to determine their affinity, potency and efficacy at the human $\beta_2$ adrenoceptor. This data will allow for the identification of structural requirements for high affinity, potent full agonists.

*1. Hit Identification and screening: Radioligand Binding Assays*
Aims:

- To determine the affinity, association rate and dissociation rate of [$^3$H]-dihydroalprenolol ([$^3$H]-DHA), a non-selective β-adrenoceptor (β-AR) antagonist, for human $\beta_2$-adrenoceptors ($\beta_2$-AR) transiently expressed in COS-7 cells.
- To characterize the $\beta_2$-AR affinity of a series of compounds based on SOMS-1, a hit identified from a library of compounds as having β2-AR affinity.

*2. Lead Modification: Structure-Activity Relationships (cAMP BRET assay)*
Aims:

- To investigate the structural basis of ligand potency and efficacy of a series of compounds (SOMS 1 – 11) for human $\beta_2$-adrenoceptors ($\beta_2$-AR) expressed in CHO-K1 cells. This data will be obtained using a BRET CAMYEL cAMP biosensor.

*3. Lead Modification: Structure-Activity Relationships (Data Analysis)*
Aims:

- To investigate the structural basis of $\beta_2$AR affinity, potency and efficacy of a series of compounds (SOMS 1 – 11).
- To determine the physicochemical properties, lipophilicity and drug-likeness of a series of compounds (SOMS 1 – 11)

*4. Computational Drug Design*

Aims:

- To characterize the amino acids that contribute to affinity, potency and efficacy of a series of $\beta_2$-AR compounds based on SOMS-1, a hit identified from a library of compounds as having $\beta_2$-AR affinity.
- To predict receptor-ligand interactions that will improve compound affinity, potency and/or efficacy

Sources of active compounds

This lecture will explore the various sources of compounds that can be used to produce libraries for screening. These sources include isolation of compounds from natural sources, combinatorial methods of organic synthesis; fragment based approaches, and privileged motifs. The advantage and disadvantages of each source will be discussed. The use of ethnopharmacology to identify new therapeutic scaffolds and drug repurposing will also be examined.

Ligand-based Drug Design

To improve the properties of a potential drug, structure-activity relationships are established to identify structural moieties that contribute to the binding and activity of a compound. Computational methods will be discussed in this lecture which can be used to model and predict these properties, and to screen databases for new leads. These methods include quantitative structure-activity relationship (QSAR) and pharmacophore determination. A pharmacophore defines the structural features and geometry of a drug that impart biological activity.

Structural biology in drug development

A fundamental requirement of structure-based drug design (also termed rational drug design) is knowledge of the 3-dimensional structure of the target, generally a protein, sometimes a nucleic acid, occasionally a protein-nucleic acid complex. In this lecture, we will explore the experimental methods available for determining these structures, focusing on X-ray crystallography, NMR spectroscopy, and mass spectrometry and role they play in drug discovery and development.

Structure-based Drug Design

Where the detailed three-dimensional structure of the protein target is available, structure-based computer-aided drug design methods can be utilised to identify and modify lead compounds. If the protein structure is not available, then computer models, based on structures of similar proteins, can be prepared and are suitable for structure-based drug design. This lecture will introduce structure-based drug design and protein modelling methods.

Bioavailability

This lecture will explore the importance of pharmacokinetics in the clinical actions of a drug and how compound structure and chemical properties effect drug absorption, distribution, metabolism and elimination. We will focus on what properties of a compound need to be optimized to improve oral availability, metabolic stability and membrane permeability. We will look at the available tools to predict these desirable qualities. We will also discuss the specialized case of drugs targeting the central nervous system and what is required to get them pass the blood brain barrier.

Pro-drugs and Drug Delivery

An inactive derivative of a known active drug may be called a prodrug and requires

transformation within the body in order to release the active drug. Prodrugs can provide improved physiochemical properties such as solubility and enhanced delivery characteristics and / or therapeutic effect. This lecture outlines barriers to drug action, pro-drugs as drug delivery systems, and the application of pharmacokinetics and pharmacodynamics in drug delivery.

Biopharmaceuticals

This lecture will introduce therapeutic proteins, also call biopharmaceuticals or biologics. In general, this includes vaccines, blood, blood components or derivatives, plasma derivatives, recombinant DNA (rDNA) products, monoclonal antibody, therapeutic serum, toxin, antitoxin, cell and gene therapy products involved in the prevention, treatment or cure of a disease or condition of human beings. A subset of these, monoclonal antibodies, antibody substitutes and fusion proteins (cytokine fusions and receptor fusions) follow a similar workflow to that employed for small molecule drugs and some of the similarities and differences in discovery and development will be highlighted.

## 3. Pre-Clinical & Clinical Development

Pre-clinical Toxicology: *In Vitro*

In this lecture the role of in vitro toxicity tests in establishing the safety of new drugs will be addressed. How the *in vitro* toxicity tests that are required by the world's regulatory bodies, including tests for genotoxicity and cytotoxicity are performed will be discussed. The role of Good Laboratory Practice in performing these tests will also be covered.

Pre-clinical Toxicology: *In Vivo*

The role of *in vivo* toxicity tests in establishing the safety of new drugs will be discussed in this lecture. The different types of *in vivo* tests in general toxicity testing, and when they are required to be performed by the regulatory bodies will be covered. The suite of safety pharmacology tests that is required will also be discussed.

Pre-clinical Toxicology Practical: Ames test

The assessment of the genotoxicity is the first step in the safety assessment of a compound. Lead compounds with optimised affinity, potency and efficacy will be assessed to determine their genotoxicity using an Ames Test.

Aims:

- To assess the *in vitro* genotoxicity of potential lead compounds being developed for a variety of indications, including COPD. Genotoxicity will be determined using *Salmonella typhimurium* TA100 in an Ames Test.

Clinical Trials

The regulation of therapeutic products and the phases (I-IV) of clinical trial that a drug must pass through before registration will be covered in this lecture.

Clinical Trial Design

This lecture will cover clinical trial design. The components of clinical trial design to be discussed will be: aims, design, controls and placebo, blinds, randomisation procedures, sample size, statistics, endpoints and ethics.

Phase I Clinical Trials Centre Site Visit

In this practical class we will be visiting the Scientia Clinical Research facility. This newly opened facility conducts early and later phase clinical trials. We will be shown the inner workings of a trial centre, meet with clinical researchers, and discuss the process of getting a patient on a trial.

Ethics of Human and Animal Experimentation

Testing of drugs in animals and humans is under strict regulation to limit any harm and distress to the research subjects. In this lecture we will discuss the ethical conduct of biomedical research, including the policies governing biomedical and animal research in Australia. The role of institutional human ethic committees and what constitutes informed consent will be discussed. The general principles for the care and use of animals for scientific purposes and the 3 R's, replacement, reduction and refinement will be covered and the role of institutional animal ethics committees will be covered.

## 4. Registration & Commercialisation

Regulatory Affairs

The role of regulatory affairs in the therapeutics industry will be discussed. The regulatory systems in Australia and the legal basis for the regulation of therapeutic products will be covered. We will discuss why the therapeutics industry is so highly regulated and the role of the regulatory affairs professional in ensuring optimal product indications and maintenance of products on the market.

Commercial Considerations: Marketing and Phase IV

Commercial considerations in drug development will be covered from target discovery, indication selection and lead identification, through safety assessments, clinical trials and marketing. What drives decisions (Go/No-Go), time-scales, program planning and the interactive perspectives of different groups in small and large pharma companies will be covered.

Intellectual Property

The basic principles underlying the protection of intellectual property will be discussed, focussing on the legal issues relevant to the patenting of pharmaceutical agents. We will discuss the types of patents available and what can be protected, the notions of disclosure, prior art, innovation, challenges, and what needs to be included in a patent application.

Careers in Drug Discovery

This workshop will take place during the practical time slot in week 12. Invited guests working in different phases of the drug development process will talk about their career path and provide insight into the jobs they do.

Case Studies in Drug Discovery

Having now journeyed from bench to bedside, we will look at the path that some drugs travelled to get to the clinical. This lecture will highlight the challenges and triumphs the drug discovery and development teams faced.

**PHAR3101 Drug Discovery, Design and Development – Timetable 2017**

| Wk | Start. Mon | Practical Tuesday 2-5pm WW | Lecture 1 Wednesday 10am WWLG02 | Lecture 2 Wednesday 2pm MacauleyTh | Tutorial-2 time slots; Wed 3pm or 4pm Webst 302 |
|---|---|---|---|---|---|
| 1 | 24/7 | Drug discovery process | Drug Discovery & Development: Choosing the project<br>A. Finch | Novel target identification and validation<br>P. Gunning | |
| 2 | 31/7 | Target validation | DNA as a drug target<br>L. Wakelin | Gene modification techniques in drug discovery<br>L. Wakelin | Novel Target identification & validation |
| 3 | 7/8 | Drug validation | Target Selection<br>A. Finch | Biological Assays: Hit Identification<br>A. Finch | Nucleic acids as targets |
| 4 | 14/8 | Hit identification and screening: radioligand binding | High-throughput screening<br>A. Finch | Sources of active compounds<br>A. Finch | Target selection |
| 5 | 21/8 | Lead Modification: Structure-Activity Relationships (cAMP BRET Assay) | Ligand-based drug design<br>A. Finch | Structural biology in drug development<br>A. Stewart | Hit identification & HTS screening |
| 6 | 28/8 | Lead Modification: Structure-Activity Relationships (Data Analysis) | **Progress Exam** | Structure-based drug design<br>A. Finch | Structure Activity Relationships |
| 7 | 4/9 | Computational Drug discovery | Bioavailability<br>A. Finch | Pro-drugs and drug delivery<br>T. Binder | Structural based drug discovery |
| 8 | 11/9 | Preclinical toxicology: Ames test (week A) | Biopharmaceuticals<br>T. Domagala | Pre-clinical toxicology – *in vitro*<br>N. Kumar | Drug Delivery and Bioavailability |
| 9 | 18/9 | Preclinical toxicology: Ames test (week B) | Pre-clinical toxicology – *in vivo*<br>N. Kumar | Clinical trials<br>N. Kumar | Sources of active compounds & Biopharmaceuticals |
| **Mid-semester break** | | | | | |
| 10 | 2/10 | Group Work | Clinical trial design<br>N. Kumar | Ethics of human and animal experimentation<br>N. Kumar | Pre-clinical toxicology |
| 11 | 9/10 | Phase I Clinical Trials | Regulatory Affairs<br>O Chisholm | Commercialisation: marketing and phase 4<br>O. Chisholm | Clinical trial design |
| 12 | 16/10 | Careers in Drug Discovery | Intellectual property<br>L. Wakelin | Case studies in drug discovery<br>A. Finch | Regulatory Affairs/ Commercialisation |
| 13 | 23/10 | | | | Drug discovery process |

## Assessment Tasks

| Task | Due Date |
|---|---|
| **Therapeutic product development history** | |
| *Part 1a:* Timeline | Monday 21st August, 9 am |
| *Part 2:* Review | Monday 9th October, 9 am |
| **Progress Exam** | Wednesday, 30th August, 10 am |
| **Research Manuscript** | Monday 11th September, 9 am |
| **Final Examination** | Official exam period |
| **Formative tasks** | Each tutorial |

## Formative Assessment

The goal of formative assessment is to provide ongoing feedback that you can use to improve your learning. Formative assessment tasks help students identify their strengths and weaknesses and therefore the areas they should focus on.

## Exams

The questions will be based on the material covered in the lectures, practical classes and tutorials**.**

**Progress examination (10%)** will be held in the lecture slot at **10 am on Wednesday the 30th of August.** This exam will give you feedback on how you are succeeding in the course. This examination consists of two parts (A & B):

- Part A consists of 3 short answer questions, each worth 10 marks. Answer 2 of these questions. If you answer more than 2 questions, only the first 2 will be marked
- Part B consists of 2 long answer questions, each worth 20 marks. Answer 1 of these questions. If you answer more than 1 question, only the first 1 will be marked.

**Final Examination (55%)** will be held in the official exam period.

The examination consists of two parts (A & B)

- Part A consists of 6 short answer questions, each worth 10 marks. Answer 4 of these questions. If you answer more than 4 questions, only the first 4 will be marked
- Part B consists of 6 long answer questions, each worth 20 marks. Answer 4 of these questions. If you answer more than 4 questions, only the first 4 will be marked

Material covered prior to the progress exam may be again examined in the final exam.

## Research Manuscript

You are to prepare a manuscript on behalf of the Somsceuticals Respiratory Disease Division using the data you have collected on the SOMS compounds during the practicals in weeks 4-6, and following the instructions below.

- Word limit 3000±300 words (excluding references, tables, figures and figure legends).

- The report should be referenced using in-text referencing in the style of British Journal of Pharmacology.

- Written assessment tasks must be submitted electronically *via* Moodle.

- The manuscript is to be submitted to the "journal editor" (through the Moodle site) by 9 am, 11th of September 2017. A 10% penalty (per working day) will apply for late submissions.

**The manuscript needs to contain the following sections:**

1. Title, Authors & Addresses
2. Introduction
3. Methods
4. Results
5. Discussion and conclusions
6. List of references
7. Tables
8. Figures and Legends

**Title, Authors and Addresses**

The title should contain no more than 150 characters (including spaces) and should not consist of more than one sentence. It must clearly indicate the subject matter of the paper. Titles should indicate broadly what the paper is about. Following the title the name (and student number) and address (Respiratory Disease Division, Somsceuticals, NSW, Australia) of the author should be given.

**Introduction**

The introduction should give a short and clear account of the background of the drug target and the rationale of the investigation. The final sentence should summarise the broad conclusions of the paper. Do not include a summary of the methods or results in the introduction. *TIP: you need to reference the prior work by Somsceuticals in regard to SOMS1-9 as (unpublished data), for example the synthesis of the compounds.*

**Methods**

Briefly describe the experiments in a few sentences for each method with reference to the practical manual *e.g.* ...as previously described (PHAR3101, 2017).

**Results**

The results section includes:

i. A written description in paragraph format of the experimental results. When results are reported, the mean results with standard errors, and the number of observations, and statistical significance should be given. Conclusions or interpretation of results should not be presented.

ii. A graph and figure legend of the competition binding data (<u>do not</u> include the saturation binding, temperature or time course graphs)

iii. A graph and figure legend of the mean % maximum isopertenolol response data

iv. A graph molecular property *vs* either $\log K_i$ or $\log EC_{50}$

v. A table of the $K_i$ and affinity relative to SOMS-1 values for each compound

vi. A table of Mean Log $EC_{50}$ ± SE, mean $EC_{50}$, Δ and relative potency for each compound

vii. A table of Molecular Properties data (*ie* miLogP, MW, nrotb, TPSA)

viii. A table of π data for each R group

ix. A figure showing the structures being investigated (this is important so your reader can understand what you are talking about when you are comparing the different "R" groups.)

x. You may also include data from week 7's practical if you wish

*Tables:* Each table should have a brief descriptive title. Each column should have a heading and the units of measurement should be given in parentheses in the heading. Use either scientific notation or general number format not both in a given column. Limit numbers to 2 decimal places. Tables should be self-explanatory, with necessary descriptions of each heading provided underneath the table.

*Figures and Legends*

Figure legends should explain the figures in sufficient detail that, whenever possible, they can be understood without reference to the text. A very brief description of the experimental method, including "n's" and statistical measurements should be included. Do not summarise your results in the figure legend.

**Discussion and Conclusions**

The purpose of the discussion is to present a brief interpretation of the results with reference to other scientific studies. Repeating the results should be avoided. The main conclusions should be conveyed in a final paragraph with a clear statement of how the study advances knowledge and understanding in the field.

*Your discussion should address the following issues*

1. What relationship if any exists between each of the functional groups and the potency, affinity and efficacy of each compound? *TIP: to do this you need to compare compounds that only differ at one R group.*

2. Do any of the molecular properties of the compounds relate to their potency, efficacy or affinity?

3. Is there a relationship between $\pi$ of specific functional groups and potency, efficacy and affinity of the compounds?

4. How do your findings compare to other research on $\beta_2$-adrenoceptor ligands? Can our knowledge of the molecular pharmacology of the $\beta_2$-adrenoceptor explain your results?

5. Do the compounds have suitable lead-like or drug like qualities?

6. Have you identified a suitable drug candidate for further development?

**Citations**

In the text, references to other work should take the form: (Bolton and Kitamura, 1983) or 'Bolton and Kitamura (1983) showed that…'

**References**

The reference list at the end of the manuscript must be arranged alphabetically according to the surname of the first author. When the surnames of first authors are identical, the alphabetical order of the surnames of subsequent authors takes precedence over the year of publication. The authors' names are followed by the year of publication in brackets. If more than one paper by the same authors in one year is cited, a, b, c, etc. are placed after the year of publication, both in the text and in the list of references. All authors should be quoted for papers with up to six authors; for papers with more

than six authors, the first six should be quoted followed by *et al*. For example:

*Journal Reference*

Connor M, Kitchen I (2006). Has the sun set on κ3-opioid receptors? Br J Pharmacol 147: 349–350.

*Book Reference*

McGrath, JC, Daly CJ (2005). Imaging adrenergic receptors and their function: the use of fluorescent ligands and receptors to visualize adrenergic receptors. In: Perez DM (ed). *The Adrenergic Receptors, in the 21st Century.* Humana Press: New Jersey, pp 65–72.

**Formatting and Technical Instructions**

Times New Roman font, size 12, with 1.5 line-spacing throughout the manuscript. Margins at top and bottom and both sides should be 3 cm. *The text should **not** be in two columns*.

**PRACTICAL REPORT: MARKING CRITERIA**

| | **Exemplary** (>8.5) | **Very Good** (8.4-7.5) | **Good** (7.4-6.5) | **Satisfactory** (6.4-5.0) | **Unacceptable** (<5.0) |
|---|---|---|---|---|---|
| **Title and Formatting** _____ **x 0.5** | Title clearly indicates the subject matter of the paper. Name and student number and departmental address given. Times roman, 12 font, 1.5 line-spacing, Margins 3 cm. Word count 3000 ± 300. | Title indicates the subject matter of the paper. Name and student number and departmental address given. Minor errors in formatting. Word count 3000 ± 300. | Title indicates the subject matter of the paper. Name and student number and departmental address given. Errors in formatting. Word count 3000 ± 300. | Title does not indicate the subject matter of the paper. Name and student number and departmental address given. Errors in formatting. Word count > 3300. | Title, author's name and/or address not given. Formatting requirements not followed. Word count >3300 or<2700. |
| **Introduction** _____ **x 2** | Concise and clear account of the scientific background and the rationale of the experiment. Final sentence summarises the broad conclusions of the paper. | Clear account of the scientific background and the rationale of the experiment. Minor omissions or errors. Final sentence summarises the broad conclusions of the paper. | A good introduction of the scientific background and the rationale of the experiment. A few factual error or omissions. Final sentence summarises the broad conclusions of the paper. | Some introduction to the scientific background and the rationale of the experiment. More detail needed. Improved summary of the major finding needed. | Lacking detail of the rationale of the experiment and scientific background. Summary of the major finding not given. |
| **Methods** _____ **x 1** | Appropriate detail and referencing of methods used. | Sufficient detail and referencing of methods used. Minor details missing. | Insufficient detail and referencing of methods used. Minor errors. | Methods given but not referenced. Lacks details and has errors. | Methods not written in paragraph style. |
| **Results** _____ **x 1** | Excellent description of the experimental results. No conclusions or interpretation of results presented. Data analysis was performed correctly. | Good description of the experimental results. No conclusions or interpretation of results presented. Minor errors in data analysis. | Good description of the experimental results. Lacks some required detail. No conclusions or interpretation of results presented. A few errors or omissions in data analysis. | Description of the experimental results lacks required detail. Some conclusions or interpretation of results presented. Some errors or omissions in data analysis. | No description of results. Results not written in paragraph style. Errors in data analysis. Some data analysis not presented. |
| **Tables, Figures & Legends** _____ **x 1** | Graph axes labelled and units of measurement given. Legends explain the figures in sufficient detail that they can be understood without reference to the text. Tables self-explanatory, with necessary descriptions provided in footnotes underneath the table | Graph axes labelled and units of measurement given. Legends explain the figures in sufficient detail that they can be understood without reference to the text. Tables self-explanatory, with footnotes underneath the table. A few minor errors in data presentation | Graph axes labelled and units of measurement given. Not all legends explain the figures in sufficient detail that they can be understood without reference to the text. Most tables self-explanatory, with footnotes underneath the table. Some minor errors in data presentation. | Most graph axes labelled and units of measurement given. Not all legends explain the figures in sufficient detail that they can be understood without reference to the text. Most tables are self-explanatory. Some significant errors in data presentation | Results poorly presented or missing. Graph axes not labelled and units of measurement absent. Legends do not explain the figures in sufficient detail that they can be understood without reference to the text. Tables are not self-explanatory. |
| **Discussion & Conclusion** _____ **x 2.5** | Discussion is clear and succinct. Extensive interpretation of the results with reference to previous scientific studies. No re-statement of the results. Main conclusions conveyed in a final paragraph. | Good interpretation of the results, greater reference to previous scientific studies needed. Some re-statement of the results. Main conclusions conveyed in a final paragraph. | Some interpretation of the results, greater reference to previous scientific studies needed. Minor errors in interpretation of the results Some re-statement of the results. Conclusions conveyed in a final paragraph. | Some interpretation of the results, greater reference to previous scientific studies needed. Errors in interpretation of the results Some re-statement of the results. Some conclusions conveyed in a final paragraph. | No interpretation of the results with reference to previous scientific studies given. Results presented. Main conclusions not conveyed in a final paragraph. |

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|---|---|---|---|---|---|
| **Referencing**<br>_____ **x 1** | In-text citations and reference list follow BJP conventions. Relevant information selected. A wide range of references used. | In-text citations and reference list follow BJP conventions. Relevant information selected. A wider range of references needed. | In-text citations and reference list follow BJP conventions, with minor errors. Relevant information selected. A wider range of references needed. | In-text citations and/or reference do not follow BJP conventions. Relevant information selected. A wider range of references needed. | BJP conventions not followed. Non-peer reviewed sources used. Information in introduction and discussion not referenced. Wider range of references needed. |
| **Writing Conventions**<br>_____ **x 1** | Excellent sentence structure, correct grammar and word usage. Sentences and paragraphs well connected. Appropriate written expression- using discipline specific vocabulary and formal not oral language. Has been proof read. | Good sentence structure, correct grammar and word usage. Sentences and paragraphs well connected. Appropriate written expression- using discipline specific vocabulary and formal not oral language. Proof reading needed to eliminate minor errors. | Good sentence structure, correct grammar and word usage. Sentences and paragraphs not always well connected. Appropriate written expression- better use of discipline specific vocabulary and formal not oral language needed. Proof reading needed to eliminate minor errors. | Poor sentence structure, grammar and word usage. Sentences and paragraphs not well connected. Appropriate written expression- better use of discipline specific vocabulary and formal not oral language needed. Proof reading needed to eliminate errors. | Use of paragraphs and improved sentence structure needed. The report is difficult to read due to poor grammar and word usage. No evidence of proof reading. |
| **TOTAL /100** | | | | | |

**Therapeutic product development history**

***Part 1: Timeline (5%)***

- Each group will produce a timeline of the drug design and development process of their drug, highlighting the major milestone in the journey that the drug took from bench to bedside. This should include at least one entry for the following stages of the drug design and development process for the given drug: (A) Target Selection, (B) Lead Discovery, (C) Preclinical Development and (D) Clinical Trials. *See below for more details of each section*
- You can be creative as you like in producing your timeline. Some suggestions are to use online timeline production freeware, a video, an animation, drawing program etc. Whichever medium you choose to produce your timeline your overall aim should be to educate your audience about the major milestones along the path your drug took from bench to bedside.
  - For instructions on how to upload your timeline multimedia file(s) please go to https://student.unsw.edu.au/using-moodle-media-collection and scroll down to the 'Submit a media collection as an assignment' section.

    Briefly; click the media collection link, on the media collection page, click Submit Assignment. On the edit submission page, choose the gallery you wish to submit in the Gallery section. Open the File submissions and/or Online text sections and add this material. Click Save changes.
- Timelines must be submitted to the 'Timeline' media gallery, by 9 am on the 21st of August, 2017. A penalty will apply for late submissions.

***Part 2: Review (10%)***

Each group will research the drug design and development process of a given drug and present the information in the form of a review (4000 words total excluding tables, figures legends and references).

- The review will cover the following stages of the drug design and development process for the given drug: (A) Target Selection, (B) Lead Discovery, (C) Preclinical Development and (D) Clinical Trials. *See below for more details of each section.*
- The review should be referenced using in-text referencing in the style of the British Journal of Pharmacology.
- Written assessment tasks must be submitted electronically *via* Moodle through Turnitin.
- The review is to be submitted by 9 am on the 9th of October 2017. A penalty will apply for late submissions.

STAGES OF DRUG DESIGN AND DEVELOPMENT PROCESS

**A. Target selection:**

In "Target selection" you should cover the information that the drug design and development team needed to know to start the process i.e. the disease they want to treat, the patho-physiological basis of the disease, why the target was chosen over other possible targets, what was known about the target (i.e. structure, signalling pathways etc.), what physiological processes the target is involved in.

**B. Lead discovery:**

Lead discovery is the next step in the process and includes topics such as lead discovery, lead modification, computer-aided drug design (i.e. pharmacophores, QSAR, docking) and screening and other assays. To research this stage, you will need to search for historical information on the compounds that led to the final development of the candidate taken into clinical trials.

**C. Preclinical development:**

Preclinical development includes a comprehensive account of in vitro and in vivo studies conducted on the candidates before they were taken into clinical trials. These will include studies in animal models of disease states. Your research should cover how the studies were done, what the compound was compared to i.e. placebo or current treatment and the results of these studies. This stage of development also includes

toxicology studies and non-human pharmacokinetics and metabolism studies.

**D. Clinical trials:**

The journey from bench to bedside of your drug will end with clinical trials. It may be difficult to find any information on phase 1 and 2 trials as they are often not published until after the drug has been approved for clinical use. However, you may find information on the pharmacokinetics of the drug (this information is generated in phase 1 and sometimes phase 2 trials). This section should summarise what trials were done, what were they comparing (i.e. drug vs. placebo or drug vs. current treatment), the types of patients recruited (i.e. the diseases they had, sometimes the one drug is trialled in the treatment of a few different conditions/syndromes etc.), and what were the outcomes (i.e. was the drug 10 times better, the same but with fewer side effects etc.), what side effects were reported in the trials. Make sure you only include trials prior to the registration of the drug; often more trials are done post registration for other indications.

**Therapeutic product development history (Part 1): Timeline**

| **Criteria** | **Exemplary** (>8.5) | **Very Good** (8.4-7.5) | **Good** (7.4-6.5) | **Satisfactory** (6.4-5.0) | **Unacceptable** (<5.0) |
|---|---|---|---|---|---|
| **Quality of content** _____ **x 2.5** | Included events are important and interesting. No major details are missing. | Most of the included events are important or interesting. One or two major events are missing. | Most of the included events are important or interesting. Some major events are missing. | Some events included are trivial, and/or major events are missing. | Most of the major events are missing, and/or too many trivial events are included. |
| **Accuracy of Content** _____ **x 2.5** | Facts are accurate for all events reported on the timeline. | Facts are accurate for almost all events reported on the timeline. | Facts are accurate for most of the events reported on the timeline. | Facts are accurate for some of the events reported on the timeline. | Facts are often inaccurate for the events reported on the timeline. |
| **Sequence of Content** _____ **x 2.5** | All events are placed in proper order. The dates included are accurate | Events are placed in proper order & most of the dates included are accurate. | Most of the events are placed in proper order & most of the dates included are accurate | Some of the events are placed in proper order & some of the dates included are accurate | Most events are incorrectly placed on the timeline and the dates not included or not accurate |
| **Audio and/or visual aids** _____**x 2.5** | Audio/visual material engages the audience. All graphics are effective and balanced with text use. The audio/visual components greatly enhanced the timeline. | Audio/visual material engages the audience. Most of the graphics are effective and balanced with text use. The audio/visual components enhanced the timeline. | Audio/visual material engages the audience. Some of the graphics are not effective or balanced with text use. The audio/visual components add to the timeline. | Audio/visual material conveys the material, but does not grab the interest of the audience. The ratio of graphics & text is not balanced | Audio/visual material does not enhance the presentation or was missing |

## Therapeutic product development history (Part 2): Review

| Criteria | **Exemplary** (>8.5) | **Very Good** (8.4-7.5) | **Good** (7.4-6.5) | **Satisfactory** (6.4-5.0) | **Unacceptable** (<5.0) |
|---|---|---|---|---|---|
| **Quality & Accuracy of content** _____ **x 3** | Included events are important & interesting. No major details are missing. The development details are accurately reported. | Most of the included events are important & interesting. One or two major events are missing. The development details mostly are reported accurately. | Most of the included events are important or interesting. Some major events are missing. The development details are mostly reported accurately. | Some events included are trivial, and/or major events are missing. The development details are accurate for most of the events reported. | Most of the major events are missing, and/or too many trivial events are included. The development details are often inaccurate for events reported. |
| **Organisation, structure & clarity** _____ **x 4** | Comprehensive review that fully explores the steps taken, challenges faced and outcomes achieved to progress through each phase of the DDDD process. | Detailed review that explores the steps taken, challenges faced and outcomes achieved to progress through each phase of the DDDD process | Review clearly outlines the steps taken, challenges faced and outcomes achieved to progress through each phase of the DDDD process | Review only superficially or incompletely explores the steps taken, challenges faced and outcomes achieved to progress through each phase of the DDDD process | Information about the steps taken, challenges faced and outcomes achieved to progress through each phase of the DDDD process is lacking from the review |
| **Presented as an integrated assignment.** _____ **x 1** | The information given in each stage is not duplicated. Each stage links to the next and overall the essay flows very well. Formatting is consistent across all sections. | Almost none of the information given in each stage is duplicated. Each stage links to the next and overall the essay flows. Most of the formatting is consistent across all sections. | The information given is duplicated across stages. Most stages link and overall the essay flows. Some formatting inconsistencies across sections. | The information given in many stages is duplicated. Lack of connection between stages and disjointed in places. Some formatting inconsistencies across sections. | No evidence of collaboration across the document. The information given is duplicated across the stages. The essay doesn't flow. Formatting not consistent across sections. |
| **Referencing** _____ **x 1** | In-text citations and reference list follow BJP conventions. Relevant information selected. A wide range of references used. | In-text citations and reference list follow BJP conventions. Relevant information selected. A wider range of references needed. | In-text citations and reference list follow BJP conventions, with minor errors. Relevant information selected. A wider range of references needed. | In-text citations and/or reference do not follow BJP conventions. Relevant information selected. A wider range of references needed. | BJP conventions not followed. Non-peer reviewed sources used. Information provided not referenced. Wider range of references needed. |
| **Writing Conventions** _____ **x 1** | Excellent sentence structure, correct grammar and word usage. Sentences and paragraphs well connected. Appropriate written expression- using discipline specific vocabulary and formal not oral language. Has been proof read. | Good sentence structure, correct grammar and word usage. Sentences and paragraphs well connected. Appropriate written expression- using discipline specific vocabulary and formal not oral language. Proof reading needed to eliminate minor errors. | Good sentence structure, correct grammar and word usage. Sentences and paragraphs not always well connected. Appropriate written expression- better use of discipline specific vocabulary and formal not oral language needed. Proof reading needed to eliminate minor errors. | Poor sentence structure, grammar and/or word usage. Sentences and paragraphs not always well connected. Appropriate written expression- better use of discipline specific vocabulary and/or formal not oral language needed. Proof reading needed to eliminate errors. | Use of paragraphs and improved sentence structure needed. The report is difficult to read due to poor grammar and word usage. No evidence of proof reading. |