Ollscoil na Gaillimhe
University of Galway

Scoil na nEolaíochtaí
Bitheacha agus Ceimiceacha

School of Biological
and Chemical Sciences

3BPC (Biopharmaceutical Chemistry)

Information Booklet

Academic Year 2024 – 2025

Compiled by Dr. David Cheung
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Contents

Welcome and General Information

Welcome to third year chemistry at the University of Galway. We look forward to working with you in your studies this year. This booklet summarises the key information about the structure and content of the third-year course, along with some important policies in the School. While every effort has been made to make sure the information in this booklet is accurate and up to date, it is inevitable that some changes to this may be needed throughout the year. These will be communicated through Canvas, the University's virtual learning environment, so please check this, along with your university email address, throughout the year. Canvas will also be used to host lecture notes and other resources.

Attendance at all timetabled lectures and tutorials is expected and will be monitored. Note that while attendance at lectures is a key part of learning, it is not on its own sufficient and you are expected to support this through independent study. For a 5 ECTS module, the total workload is expected to be in the range of 100-125 hours, so for each lecture you may expect to have undertake three to four hours of self-study.

Attendance at laboratory sessions is mandatory. For short term absences (e.g. through illness) authorized absences may be obtained by submitting appropriate documentation – this should be sent to the module coordinator and the school administrators. For absences due to sports or societies activities, you must contact the module coordinator in advance of these. If you are unfortunate to be absent for a longer period of time please refer to the university's extenuating circumstances policy (https://www.universityofgalway.ie/media/registry/exams/policiesprocedures/QA209-Extenuating-Circumstances.pdf).

While we hope that you will not encounter any difficulties, academic or thoerwise, during this year, the university has a range of supports in areas including adacmis skills, health, and finance. A guide to these is available here (https://www.universityofgalway.ie/media/collegeofscienceandengineering/CSE_StudentSupportMap_V.5_ColourblindFriendly-3.pdf).

You are expected to adhere to the university academic integrity policy (**https://www.universityofgalway.ie/media/registrar/docs/QA220-Academic-Integrity-Policy-Final.pdf**). Note that the unauthorised use of Artificial Intelligence is not permitted in assessments. Please check with your instructor if you have any questions about what is or is not allowed to be used.

Course Structure and Schedule

	Module (ECTS Credits)	Examination/Assessment	
		Two-Hour Exam Paper	Continuous Assessment
Semester I	CH311 - Organic Chemistry (5)	80%	20%
	CH326 - Analytical Chemistry & Molecular Structure (5)	80%	20%
	CH332 - Drug Design & Drug Discovery (10)	50%	50%
	CH333 - Experimental Chemistry I (5)	-	100%
	BI319 - Molecular Biology (5)	60%	40%
Semester II	CH307 - Inorganic Chemistry (5)	80%	20%
	CH313 - Physical Chemistry (5)	80%	20%
	CH334 - Experimental Chemistry II (5)	-	100%
	CH3103 - Validation in the Pharmaceutical and Medical Devices Industry (5)	65%	35%
	BI317 - Human Molecular Genetics (5)	80%	20%
	BI321 - Protein Biochemistry (5)	60%	40%
CH4106 - Work Placement (20) – See details on pages 18-19			

Semester I Schedule

CH311 First lecture in Dillon Theater on Monday, September 9th 2024, at 9am

CH326 First lecture in Dillon Theater on Friday, September 13th 2024, at 10am

CH332 First lecture in Dillon Theater on Tuesday, September 10th 2024, at 9am
First practical class on Monday, September 16th 2024, at 2pm (details on registration and final timetable to be provided in due course)

CH333 First practical class in Organic Chemistry Teaching Laboratory on Tuesday, September 17th 2024, at 2pm (details on registration and final timetable to be provided in due course)

Semester II Schedule - To be confirmed in due course

Details on Biochemistry Modules are available online at https://www.universityofgalway.ie/course-information/module/BIxxx

While every effort has been made to ensure that this booklet is accurate, students should contact Module Coordinator(s) with queries. Any updates will be communicated through Canvas

Key Contacts

3rd year coordinator – Dr David Cheung (david.cheung@universityofgalway.ie)

Chemistry Pathway coordinator – Constantina Papatriantafyllopoulou (constantina.papatriantafyllopo@universityofgalway.ie)

Head of the School of Biological and Chemical Sciences – Prof. Olivier Thomas (olivier.thomas@universityofgalway.ie)

Chemistry adminstrators – Karen Kelly (karen.kelly@universityofgalway.ie), Judy Buckley (judy.buckley@universityofgalway.ie)

Module coordinators

CH311 Organic Chemistry – Prof. Paul Murphy (paul.murphy@universityofgalway.ie)

CH326 Analytical Chemistry and Molecular Structure – Dr Mihai Lomora (mihai.lomora@universityofgalway.ie)

CH333 Experimental Chemistry I – Dr Binh Mai (binh.mai@universityofgalway.ie)

CH332 Drug Design and Drug Discovery – Dr David Cheung (david.cheung@universityofgalway.ie)

CH307 Inorganic Chemistry – Dr Luca Ronconi (luca.ronconi@universityofgalway.ie)

CH313 Physical Chemistry – Dr Chong-Wen Zhou (chongwen.zhou@universityofgalway.ie)

CH334 Experimental Chemistry II – Dr Luca Ronconi (luca.ronconi@universityofgalway.ie)

CH3103 Validation in the Pharmaceutical and Medical Devices Industry - Dr Constantina Papatriantafyllopoulou (constantina.papatriantafyllopo@universityofgalway.ie)

BI317 Human Molecular Genetics – Prof. Brian McStay (brian.mcstay@universityofgalway.ie)

BI321 Protein Biochemistry – Dr Maria Tuohy (maria.tuohy@universityofgalway.ie)

CH311 - Organic Chemistry

Instructors: Prof. Paul Murphy (Module coordinator), Prof. Peter Crowley, Dr Eddie Myers

MODULE DELIVERY

1. Physical Organic Chemistry, Reaction Mechanism (10 h + 2 h tutorial, PM)

At the end of this lecture series students should be able to:

- Write expressions for K_a and pK_a.
- Use K_a and pK_a to draw conclusions about acid and base strength.
- To know or predict a molecule or functional groups protonation state at a defined pH.
- To understand and explain chemical factors that affect acidity and basicity.
- To be able to relate pK_a to other properties (*e.g.* leaving group ability, nucleophilicity).
- To understand how various types of experiments are used to study reaction mechanism, including kinetics, kinetic isotope effects, substituent effects (Hammett plots & LFERs), product identification, trapping & competition experiments, cross-over experiments, isotope scrambling & labelling, stereochemical analysis, computational methods.
- To be able to write reasonable mechanisms for well-known reactions such as acid- and base-promoted hydrolysis of esters; acid-catalyzed formation/hydrolysis of acetals/ketals.
- To solve problems based on the material covered.

2. Biomolecular Chemistry (10 h + 2h tutorial, PC)

This aspect of the course focuses on biological molecules in particular, proteins. "*Foundations of Chemical Biology*" (Oxford Primer) is an excellent textbook that will also be useful for fourth year.

Amino acids, peptides and proteins

- Structures and properties of the amino acids.
- Primary, secondary, tertiary and quaternary structures of proteins.
- Isoelectric point.
- The hydrophobic effect.
- Interactions between proteins and small molecules (*e.g.* carbohydrates, lipids).

Carbohydrates

- Monosaccharides: classification and configuration.
- Reactions at the anomeric center.

Lipids

- Biological lipids, bilayers and membranes.
- Chemical structures of terpenes and steroids.

3. Synthesis and Stereochemistry (10 h + 2 h tutorial, EM)

Synthesis

- A general understanding of what organic synthesis involves, and of the difficulties associated with the synthesis of a polyfunctional molecule which can exist in different stereoisomeric forms.
- An understanding of the reason why the synthesis of a complex organic molecule is undertaken.
- A recognition of the different classes into which syntheses can be divided.
- The ability to calculate the yield of a multistep synthesis.
- The ability to distinguish between linear and convergent syntheses, and an appreciation of the advantages of the former.
- An understanding of the basic concept underpinning retrosynthetic analysis.
- The ability to describe what the following terms involve and to provide simple examples of each one: disconnection, functional group interconversion, synthon, synthetic equivalents.
- The ability to carry out multistep retrosynthetic analyses based on the use of Grignard reactions, redox reactions involving carbonyl groups, catalytic hydrogenation, alkyl halide/alcohol interconversions, Friedel-Craft reactions, aldol reactions and Michael reactions.
- The ability to carry out the retrosynthetic analyses of six-membered carbocylic rings based on Diels-Alder reactions and Robinson annulations.
- A general understanding of the protecting group approach, of why it may be necessary, of what is involved, and of the disadvantages associated with it.
- An understanding of the circumstances under which the carbonyl groups in ketones and aldehydes need to be protected, and of how this is done.
- An understanding of the circumstances under which alcohol groups need to be protected, and of how this is done.

Stereochemistry

- The ability to distinguish between constitutional isomers and stereoisomers.
- An understanding of the difference between conformational and configurational stereoisomers.
- An understanding of the stereochemical possibilities, chirality/enantiomerism, in systems containing one asymmetric carbon.
- An appreciation of the concepts of absolute configuration, specific rotation and enantiomeric excess.
- The ability to interpret the significance of the stereochemical descriptors, (+), (-), R and S, both on their own and in combination.
- An understanding of the structural possibilities in systems containing more than one asymmetric carbon: identical, enantiomers and diastereomers.
- A recognition of the importance of a plane of symmetry in a molecule: meso stereoisomers.
- The ability to define and recognize racemization, epimers, epimerization and anomers.
- The recognition that chirality can arise in molecules containing tetrahedral atoms other than carbon: sulfoxides, etc.
- The recognition that chirality can arise in non-tetrahedral systems: allenes, atropisomers (biphenyls), helicenes.
- An understanding of the concept of resolution, the separation of enantiomers.
- The ability to describe, and to discuss the advantages and disadvantages of the three methods by which resolution can be achieved: mechanical separation, decomposition and the use of a resolving agent.
- The ability to recognize and distinguish between enantioselective and diastereoselective reactions.
- The ability to describe a number of diastereoselective reactions and to explain why they are stereoselective.
- An appreciation of why the synthesis of chiral molecules (asymmetric synthesis) is important.
- An understanding of the difficulties involved in carrying out reactions with chiral molecules in terms of retaining chirality.
- An appreciation that there are three different methods of making a chiral molecule: starting with a chiral pool molecule, carrying out a resolution, or using an enantioselective reaction.
- The ability to describe, and to discuss the advantages and disadvantages of, asymmetric synthesis involving chiral pool molecules.
- The ability to describe, and to discuss the advantages and disadvantages of, asymmetric synthesis involving resolution.
- The recognition that enantioselective reactions occur under the influence of a chiral group (chiral auxillary) which can be in the reagent, the substrate or the catalyst.
- The ability to provide examples of all the above methods of carrying out asymmetric synthesis.

Related practicals are included in the laboratory-based Module CH333 - Experimental Chemistry I. Experience will be gained in a range of synthetically important reactions, techniques associated with biological chemistry, as well as analytical techniques, both spectroscopic and chromatographic. Molecular modelling and database searching are also introduced (see description of the CH333 Module for details).

CH326 - Analytical Chemistry & Molecular Structure

Instructors: Dr Mihai Lomora (Module coordinator), Dr Andrea Erxleben, Prof. Olivier Thomas

MODULE DELIVERY

1. **Fluorescence, Advanced Chromatography, Atomic Absorption Spectroscopy (12 lectures + 1 tutorial, ML)**
   - *Fluorescence (FL)*
     - To understand basic principles of fluorescence: phenomena, Jablonski diagram, characteristics of fluorescence excitation, emission, quenching
     - To discuss properties of fluorophores, concepts such as quantum efficiency, excitation/emission wavelengths.
     - To identify typical fluorescence spectroscopy and related instrumentation and its applicability to fluorescence measurements and spectra interpretation.
   - *Advanced Chromatography (AdvChrom)*
     - To expand on the fundamental chromatographic principles.
     - To understand key parameters for chromatographic method optimisation.
     - To identify the need for isocratic vs gradient modes.
     - To analyse the role of molecular weight, solvent composition, sample injection volume, or tubing geometry in the separation process.
     - To appreciate the importance of parameters such as solvent composition, pH, temperature on the separation efficiency.
     - To identify the impact of logP on the retention mechanism, resolution and separation efficiency.
     - To apply concepts of method optimisation from a practical point of view using real separation examples.
   - *Atomic Absorption Spectroscopy (AAS)*
     - To illustrate the fundamental concepts of atomic absorption
     - To describe the operation of atomic absorption spectrometer instruments in relation to light source, atomizer, monochromator, detector, data analysis
     - To illustrate the applicability of AAS in the identification and quantification of elemental composition of various samples.

2. **Mass Spectrometry (5 lectures + 1 tutorial, OT)**
   - A basic understanding of the workings of the basic forms of mass spectrometer including:
     - Sample introduction (direct insertion probe, GC, LC systems).
     - Ionization methods (electron impact, chemical, electrospray, laser desorption).
     - Mass analyzers (magnetic sector, double focusing including kinetic filter, time of flight including reflectron, quadrupolar).
     - Ion detection.
   - An understanding of the basics of fragmentation, when and how it occurs and its prevalence with different molecule types and ionization techniques.
   - An ability, given a molecule and its mass spectrum (EI or CI) to deduce the fragmentations, and their mechanisms, leading to the main peaks; fragmentations covered will center on alpha radical initiated cleavage, adjacent bond cleavage, and McLafferty type rearrangement.
   - An understanding and ability to recognize or apply the isotope effect.
   - An appreciation of the importance of resolution as applied to HRMS.

3. **Nuclear Magnetic Resonance (NMR) Spectroscopy (7 lectures + 1 tutorial, OT)**
   - An understanding of how some nuclei, behaving like tiny bar magnets, can line up with and against an external magnetic field and so exist in two energy states.
   - An understanding of how the size of the external field affects the energy gap between these two states.
   - The ability to describe how an NMR spectrum of a molecule is obtained in terms of the basic structure of the spectrometer and of sample preparation.
   - An understanding of how the environment of a nucleus in a molecule affects the signal it produces and that thus the environment of a nucleus in a molecule can be determined from the signal it produces.
   - An understanding that the electron cloud surrounding the nucleus lowers the effective magnetic field in the vicinity of the nucleus, thus shielding it.
   - The ability to characterize signals in an NMR spectrum as being shielded/upfield/low frequency or deshielded/downfield/high frequency.
   - The ability to recognize the effect of symmetry on the number of sets of chemically equivalent protons and thus on the number of signals produced by a molecule.

- The ability to predict the number of signals that would be observed in the ^{1}H NMR spectrum of a molecule on the basis of its structure.
- An understanding that the position, or frequency, of a signal in the spectrum is determined relative to that of a standard and is referred to as the chemical shift (δ) of the signal and/or of the nucleus responsible for it.
- The ability to use a ^{1}H NMR correlation table to relate the δ value of a signal to the type of proton responsible for it.
- The ability to use the integration (area) of the signals in a ^{1}H NMR spectrum to determine the relative number of protons responsible for each signal.
- An understanding that the splitting of a signal for a proton is due to an interaction (scalar coupling) of that proton with the protons attached to the atom (usually a carbon atom) next to the atom (again usually a carbon atom) carrying the proton producing the signal.
- The ability to deduce the number of protons on an adjacent carbon based on the multiplicity of the splitting shown by a particular proton (none, doublet, triplet, quartet), given that the multiplicity is equal to (2n +1), where n is the number of protons on the adjacent carbon.
- An understanding that the standard form of ^{13}C NMR spectrum does not show C-H coupling and, thus, consists of a series of lines in which each set of chemically equivalent carbons appears as a single line.
- An appreciation that the chemical shift of a carbon signal is affected by the same factors that determine the shift of a proton signal.
- The ability to use a ^{13}C NMR correlation table to relate the δ value of a signal to the type of carbon responsible for it.
- The ability to determine the number of hydrogens attached to a particular carbon using a ^{13}C NMR DEPT spectrum.
- The ability to deduce the structure of simple molecules based on NMR data, usually in the form of actual spectra, the above concepts and simple spectroscopic correlation tables.
- An appreciation of the existence of long-range and geminal coupling, and of the concept of diastereotopic protons.
- An appreciation of the issues relating to the ^{1}H NMR spectra of molecules containing N-H and O-H bonds.

4. Crystal Diffraction (7 lectures + 1 tutorial, AE)

- An understanding of the following terms: unit cell, crystal system, Bravais lattice, space group, Miller indices.
- An understanding of the information that can be obtained from X-ray powder diffraction data.
- The ability to index simple X-ray powder diffraction patterns and to calculate the unit cell parameters from X-ray powder data of cubic structures.
- An understanding of the relevance of polymorphism.

The practicals related to the topics dealt with within the course are included in the laboratory-based Module CH333 - Experimental Chemistry I (see description of the CH333 Module for details).

CH332 - Drug Design & Drug Discovery

Instructors: Dr David Cheung (Module coordinator), Dr Laura Cunningham, Prof. Olivier Thomas

MODULE DELIVERY

The Module is delivered in 24 lectures (2 one-hour lectures per week).

1. **Computational Approaches to Drug Design (12 lectures, DC)**
   - Role of modelling in drug design.
   - Describing molecular structure.
   - Molecular Models and Force Fields.
   - Molecular Docking.
   - Challenges of modelling proteins and prediction of protein structure.
   - Molecular Dynamics.
   - Thermodynamics of protein-ligand binding.

   Learning outcomes

   At the end of this course students will be able to:
   - Describe the applications of molecular modelling in drug design.
   - Discuss the origin of the potential energy surfaces and relate features of this to the conformation of molecules.
   - Explain the different terms in a typical molecular mechanics force field
   - Describe Molecular Docking and its use in drug discovery
   - Discuss the different levels of protein structure and methods for prediction of this.
   - Describe the application of molecular dynamics simulation to investigate biomolecular structure and function
   - Critically analyze literature on the use of molecular modelling in drug design.

   Continuous Assessment

   Continuous assessment for the Computational Approaches to Drug Design component will take place across the course. The principal objectives of the course are:
   - To develop a practical capability to visualize and modify molecular structures on a computer.
   - To be able to compute binding energies.
   - To be able to analyze data from MD simulations.
   - To illustrate the principles dealt with in the lecture course.

   Recommended readings

   Students may consult the following textbooks (available in the library):
   - A.R. Leach, *Molecular Modelling: Principles and Applications*
   - A: Hinchliffe, *Molecular Modelling for Beginners*

2. **Natural Products in Drug Discovery (6 lectures, OT)**

   This lecture series covers relevant topics relating to modern natural products chemistry and its role in drug discovery and development. Main outcomes are:
   - Historical and current importance of natural products as drugs and drug leads, anti-infective, anticancer but also others.
   - The most important natural sources for bioprospection and drug discovery: plants, microbes.
   - Natural product chemistry: principles for the extraction, isolation and structure elucidation steps.
   - Basic concepts of bioactivity guided isolation process.
   - Main metabolic pathways leading to specialized metabolites or natural products.
   - New perspectives for natural products in drug discovery: sources like the marine biodiversity, extreme environments; dereplication processes, collaborative databases.

   Continuous Assessment

   The Natural Products Chemistry practical component will take place over a six-week period (2 groups, 3 laboratory sessions each, 3 h per week). Attendance records are taken at practical classes and performance will be assessed at the end of the practical. Part of the marks will be awarded for this Continuous Assessment.
   - Extraction of the metabolites from a common marine macroalga *Halidrys siliquosa*.
   - Fractionation of the extract into families of metabolites of different polarities. Use of solid phase extraction and applications of basic principles of chromatography: normal and reversed phase. Polarity of solvents.

- Analysis of some fractions by mass spectrometry and nuclear magnetic resonance. Drawing of the isolated molecules and structure elucidation.
- Propose metabolic pathways of the isolated metabolites based on basic rules.

Recommended readings

Students may consult the following textbooks (available in the library):

- P.M. Dewick, *Medicinal Chemistry, a Biosynthetic Approach*
- G.M.L. Cragg; D. Kingston, D.J. Newman, *Anticancer Agents from Natural Products*

3. Heterocycles and Solid Phase Synthesis in Drug Discovery and Design (6 lectures, LC)

Part 1 outline the importance of heterocycles as key structural motifs in drug design. In part 2, lectures will discuss the role of solid phase synthesis in drug discovery. The course will cover the following topics:

- Introduction to heterocycles and a survey of some key heterocycles found in approved drugs and in drug discovery programs.
- Nucleophilicity and reactivity of various saturated and heteroaromatic systems, stereoelectronic effects.
- The concept of isosteres, examples of commonly applied isosteres
- The principles of solid phase synthesis, including the design and use in a synthetic route
- Combinatorial and parallel synthesis as approaches to drug discovery

Learning outcomes:

At the end of this course students will be able to:

- Identify, name and discuss key reactivity of various heterocycles
- Outline the effect of heteroatoms on structure and reactivity of cyclic compounds
- Identify aromaticity according to Huckle's Rules, evaluate the relative nucleophilicity and reactivity of different hetereocycles
- Evaluate unseen drug compounds, draw reasonable isosteres and explain why they may exhibit improved pharmacokinetic or pharmacodynamic properties.
- Describe the advantages and limitations of solid phase synthesis versus traditional synthetic approaches
- Outline the key aspects of how solid phase synthesis works, and describe various considerations when designing a route that include solid phase synthesis
- Understand the core differences between parallel and combinatorial synthesis and highlight the relative benefits and disadvantages of each method.

CH333 - Experimental Chemistry I

Instructors: Dr Binh Mai (module coordinator), Prof. Peter Crowley, Dr Roisin Doohan, Dr Andrea Erxleben, Gerard Fahy, Dr Mihai Lomora, Dr Eddie Myers, Prof. Paul Murphy, Prof. Olivier Thomas

COURSE OUTLINE WITH LEARNING OUTCOMES

This laboratory-based Module complements the 3rd Year Organic Chemistry (CH311) and Analytical Chemistry & Molecular Structure (CH326) lecture-based Modules (which students **must** also take).

Attendance to laboratory sessions is **mandatory**.

On successful completion of this Module, the learner will be able to:

- Demonstrate an understanding in protein handling and purification.
- Demonstrate competence in setting up organic and organometallic reactions, work up and standard purification techniques, such as distillation, chromatography and recrystallization.
- Demonstrate competence in mole and yield calculations.
- Demonstrate competence in reaction rate monitoring and reporting.
- Demonstrate competence in organic compound characterization techniques, and analysis of spectroscopic data such as HPLC, GC, IR, UV, MS and NMR spectroscopy.
- Demonstrate competence in report writing, interpretation of laboratory results, and relate experimental data with theoretical and mechanistic aspects covered in the associated lectures (*i.e.* Modules CH311 and CH326).
- Carry out procedures in solving crystal structures.
- Demonstrate competence in the thermal analysis of polymers.

The Module is graded through Continuous Assessment by submission of written reports to laboratory class supervisors with each experiment graded out of 100%.

CH307 - Inorganic Chemistry

Instructors: Dr Luca Ronconi (Module coordinator), Dr Pau Farras, Dr Constantina Papatriantafyllopoulou,

COURSE OUTLINE WITH LEARNING OUTCOMES (LO)

This Module will provide insights into the specific roles of metals and ligands in the broad field of coordination chemistry. Specific areas to be discussed include the coordination and organometallic chemistry of transition metals and f-block elements, inorganic kinetics, and principles of nuclear chemistry.

The associated practical component of the course is carried out as part of the laboratory-based Module CH334 - Experimental Chemistry II (see description of the CH334 Module for details).

On successful completion of this Module, the learner will be able to:

LO1 explain the bonding and structural features of transition metal coordination compounds based on the Crystal Field Theory (CFT) and the Molecular Orbitals (MOs) models;
LO2 explain the structure, bonding and reactivity of transition metals in the various oxidation states;
LO3 predict the spectroscopic properties of transition metal coordination compounds using theoretical models;
LO4 discuss the mechanisms of dissociative, associative and interchange reactions of selected transition metals, including the interpretation of kinetic data;
LO5 describe the structure, bonding and reactivity of organometallic complexes;
LO6 classify the types of organometallic complexes on the basis of the coordinated ligands;
LO7 illustrate the catalytic activity of selected organometallic complexes and draw the associated mechanisms of reaction;
LO8 correlate the general features of lanthanides and actinides to their reactivity, coordination and organometallic chemistry;
LO9 recognize the basic principles of radioactivity and nuclear chemistry, to include radioactive decays, the interaction of radiations with matter, nuclear reactions and common applications of radioisotopes.

MODULE DELIVERY

The Module will be delivered in 30 lectures (normally 3 one-hour lectures per week) and 3 one-hour tutorials (normally grouped at the very end of the course). 3 one-hour duration in-class tests (making up for the Continuous Assessment component of the Module, worth 20% the overall final mark) will be held during the teaching semester according to the timetable provided.

Specifically, the following topics will be dealt with.

1. **Introduction to 3rd Year Inorganic Chemistry Laboratory (2 lectures, LR1)**
   This lecture series will provide a general introduction to the experimental work to be carried out, with a focus on the following practical experiments:
   - investigation of the oxidation states of vanadium;
   - oxidation of ethanol by Cr(VI);
   - synthesis and characterization of acetylacetonate derivatives of V(IV) and Cu(II);
   - investigation of the aqueous chemistry of Fe(III), Fe(II), Cu(II) and Ag(I);
   - the cycle of copper.

   See description of the CH334 Module for details.

2. **Coordination Compounds and their Properties (10 lectures + 1 tutorial, PF)**
   This lecture series will deal with the exploitation of the Crystal Field Theory (CFT) and the Molecular Orbitals (MOs) models to explain the properties of transition metal coordination compounds.
   Specifically, the following topics will be covered:
   - calculation of the crystal field stabilization energies for coordination compounds of the transition metals in a variety of oxidation states, using a number of common ligands and for common geometries;
   - exploitation of laboratory measured properties in conjunction with CFT to predict the geometry adopted by coordination compounds of transition metals in a variety of oxidation states, using a number of common ligands;
   - use of the point group character tables and orbital repulsion considerations to explain the d orbital splitting patterns and the symbolism used in labelling for common geometries found in coordination compounds of the transition metals;
   - drawing of MOs energy level diagrams and pictorial representations for the bonding in coordination compounds with σ-donor, π-donor and π-acceptor ligands;
   - correlation of MOs diagrams with spectroscopic properties of coordination compounds and accounting for the order of ligands in the spectrochemical series;
   - description of the dissociative, associative and interchange mechanisms for substitution reactions in coordination compounds;
   - interpretation of kinetic data in terms of the type of mechanism.

3. **Organometallic Chemistry and f-Block Elements (10 lectures + 1 tutorial, CP)**
   This lecture series will deal with the structure, bonding and reactivity of organometallic complexes, and the chemistry, properties and applications of the f-block elements.
   Specifically, the following topics will be covered:
   - description and classification of the most common types of organometallic complexes based on the various organic ligands (*e.g.* CO, NO, PR_3) used in their construction;
   - the 18-electron rule, its limitations, and its application to organometallic species;
   - description of the common reaction mechanisms observed for organometallic complexes (*e.g.* β-H elimination, alkyl migration, oxidative addition);
   - the catalytic activity of selected organometallic complexes (*e.g.* Grubbs and Schrock types) and the associated mechanisms of reaction.
   - general features of lanthanides and actinides (electron configuration, properties of the f orbitals, lanthanoid and actinoid contraction and their consequences, oxidation states and their stability in water, simple binary derivatives);
   - lanthanides and actinides complexes (aqua complex ions, common coordination and organometallic compounds, coordination numbers and geometries);
   - applications of lanthanides (redox reagents and catalysts in organic reactions, MRI contrast agents, shift reagents, luminescent sensors).

4. **Nuclear and Isotopic Chemistry (8 lectures + 1 tutorial, LR2)**
   This lecture series will deal with the basic concepts of nuclear chemistry and radioactivity.
   Specifically, the following topics will be covered:
   - the nuclear structure and its involvement in the origin of radioactivity and nuclear reactions;
   - the nuclide symbolism and definitions (isotopes, nuclear binding energy, nuclei stability band, half-life);
   - the radioactive decays and the interaction of radiations with matter;
   - radiation measurement and detection;
   - natural radioactivity and the radioactive series;
   - nuclear reactions (fission and fusion) and nuclear waste handling and cleanup;
   - isotopic labelling;
   - applications of radioisotopes (radiotracers, radiometric dating, nuclear medicine).

RECOMMENDED TEXTBOOKS AND REFERENCE MATERIAL

- C.E. Housecroft, A.G. Sharpe, *Inorganic Chemistry*, 5th Ed., Pearson Education Ltd.: 2018
- S. Cotton, *Lanthanide and Actinide Chemistry*, John Wiley & Sons Ltd.: Chichester, 2006
- Lecture notes, slides and literature papers provided in due course on Canvas

CH313 - Physical Chemistry

Instructors: Dr Chong-wen Zhou (Module coordinator), Dr David Cheung, Prof. Henry Curran, Prof. Donal Leech

TEXTBOOK

P.W. Atkins, J. De Paula, *Elements of Physical Chemistry*, 5th Ed. (available in the library)

MODULE DELIVERY

1. Molecular Interactions (5 h, HC, Chapter 15 of the textbook)

Students will understand that:

- Van der Waals force is an attractive interaction between closed-shell molecules with a potential energy that is inversely proportional to the sixth power of the separation.
- A polar molecule is a molecule with a permanent electric dipole moment; the magnitude of the dipole moment is the product of the partial charge and the separation.
- Dipole moments are approximately additive.
- The equations for potential energies of interaction for (i) charge/charge, (ii) charge/dipole, (iii) dipole/dipole, (iv) London (dispersion) interaction.
- A hydrogen bond is an interaction of the form X–H···Y, where X and Y are N, O, or F.
- The Lennard-Jones (6,12)-potential is a model of the total intermolecular potential energy.

2. Spectroscopy (10 h, CZ, Chapter 19 of the textbook)

Students will understand that:

- Energy is quantised, with transitions allowed between energy states
- The Beer-Lambert law relates intensity of absorption of radiation to concentration of the absorbing species
- The Franck-Condon principle states that because nuclei are much more massive than electrons an electronic transition takes place faster than the nuclei can respond.
- A selection rule is a statement about when the transition dipole is non-zero.
- A gross selection rule specifies the general features a molecule must have if it is to have a spectrum of a given kind. The gross selection rule for MIR absorption is that there must be a change in dipole moment during the motion for the vibration to be IR active. For Raman spectroscopy there must be a change in polarizability for the molecule/vibration to be Raman active
- A specific selection rule is a statement about which changes in quantum number may occur in a transition. The specific selection rule for vibrational spectroscopy is $\Delta v = \pm 1$.
- The vibrational energy levels of a molecule are given by:
- $E_\upsilon = (\upsilon + 1/2)hc\tilde{\nu}$, where $\tilde{\nu} = \frac{1}{2\pi c}\sqrt{\frac{k}{\mu}}$
- μ = effective or reduced mass, for a diatomic AB, $\mu = m_A m_B/(m_A + m_B)$
- The number of vibrational modes for a non-linear molecule is 3N-6, for a linear molecule it is 3N-5 where N is the number of atoms in the molecule.
- Fluorescence is the spontaneous emission of light from molecules where the transitions occurs from states of the same multiplicity.
- Phosphorescence is the spontaneous emission of light from molecules where the transitions occurs from states of the different spin multiplicity.
- A spectrometer consists of a source of radiation, a dispersing element, and a detector.
- One contribution to the linewidth is the Doppler effect, which can be minimized by working at low temperatures. Another contribution to linewidth is lifetime broadening: $\delta E \approx \hbar/T$, where T is the lifetime of the state.
- The intensity of a transition is proportional to the square of the transition dipole moment.
- A selection rule is a statement about when the transition dipole is non-zero.
- A gross selection rule specifies the general features that a molecule must have if it is to have a spectrum of a given kind.
- A specific selection rule is a statement about which changes in quantum number may occur in a transition.
- The rotational energy levels of a linear rotor and a spherical rotor are given by E_J = hBJ(J+ 1) with J = 0, 1, 2, ..., where B = fl/4nl is the rotational constant of a molecule with moment of inertia I.
- The Pauli principle states for fermions Ψ(B,A)= - Ψ(A,B) and for bosons Ψ(B,A) = Ψ(A,B). The consequences of the Pauli principle for rotational states are called nuclear statistics.

- The populations of rotational energy levels are given by the Boltzmann distribution in connection with noting the degeneracy of each level.
- The gross selection rule for rotational transitions is that the molecule must be polar.
- The specific selection rules for rotational transitions are ΔJ = ±1, ΔK = 0; a rotational spectrum of a polar linear molecule and of a polar symmetric rotor consists of a series of lines at frequencies separated by 2B.
- In a Raman spectrum lines shifted to lower frequency than the incident radiation are called Stokes lines and lines shifted to higher frequency are called anti-Stokes lines.
- A Raman spectrometer consists of a monochromatic light source (usually a laser), sampling optics, a dispersive element (spectrometer), and a detector (usually a multi-channel CCD).
- The gross selection rule for rotational Raman spectra is that the polarizability of the molecule must be anisotropic.
- The specific selection rules for the rotational Raman transitions of linear molecules are ΔJ = +2 (Stokes lines), ΔJ = -2 (anti-Stokes lines).
- The vibrational energy levels of a molecule $E_v = (v + 1/2)hcv$ with v = 0, 1, 2,..., where $v= (1/2\pi c\}(k/\mu)^{1/2}$ and $\mu = m_A m_B/(m_A + m_B)$.
- The gross selection rule for vibrational absorption spectra is that the electric dipole moment of the molecule must change during the vibration.
- The specific selection rule for vibrational transitions is Δv = ±1.
- The number of vibrational modes of non-linear molecules is 3N-6; for linear molecules the number is 3N-5.
- Rotational transitions accompany vibrational transitions and split the spectrum into a P branch (ΔJ = -1), a Q branch (ΔJ = 0), and an R branch (ΔJ = +1). A Q branch is observed only when the molecule possesses angular momentum around its axis.
- The gross selection rule for the vibrational Raman spectrum of a polyatomic molecule is that the normal mode of vibration is accompanied by a changing polarizability.
- The exclusion rule states that if the molecule has a center of inversion, then no modes can be both infrared and Raman active.

3. Electrochemistry (10 h, DL, Chapter 16 of the textbook)

Students will understand that:

- The molar conductivity of a strong electrolyte follows the Kohlrausch law
- Protons migrate by the Grotthus mechanism in aqueous solutions
- Conductivity measurements can be used to predict values of equilibrium constants for processes that produce or consume ions, such as acid dissociation
- A galvanic cell is an electrochemical cell in which spontaneous chemical reactions produces a potential difference
- An electrolytic cell is an electrochemical cell in which an external source of current is used to drive a non-spontaneous chemical reaction
- Cell potentials are related to the reaction Gibbs energy, and standard cell potentials can be used to predict thermodynamic functions (Gibbs energy, entropy, enthalpy and equilibrium constant) of processes
- The cell potential is related to concentration of species by the Nernst equation
- To induce electrolysis, the applied potential difference must exceed the cell potential at least by the cell overpotential
- Cell overpotential is the sum of the overpotentials at the anode and the cathode, and of the ohmic (iR) drop.
- An electric double layer consists of a sheet of positive charge at the surface of the electrode and a sheet of negative charge next to it in the solution (and vice versa).
- The Galvani potential difference is the potential difference between the bulk of the metal electrode and the bulk of the solution.
- The current density, j, at an electrode is expressed by the Butler-Volmer equation, $j = j_0 \left\{ e^{(1-\alpha) f\eta} - e^{-\alpha f\eta} \right\}$, where μ is the overpotential $\eta = E' - E_i$, α is the transfer coefficient, and i_0 is the exchange current density.
- A Tafel plot is a plot of the logarithm of the current density against the overpotential; the slope gives the value of α and the intercept at $\eta = 0$ gives the exchange-current density.
- Voltammetry is the study of the current through an electrode as a function of the applied potential difference.
- To induce current to flow through an electrolytic cell and bring about a non-spontaneous cell reaction, the applied potential difference must exceed the cell emf by at least the cell overpotential.

4. Self Assembly and Macromolecules (10 h, DC, Chapter 16 of the textbook)

At the conclusion of this block of lectures students will be able to:

- Give the criteria for self-assembly.
- Discuss the formation of surfactant micelles as an example of self-assembly.
- Predict the morphology of surfactant aggregates based on the relative geometries of the head and tail groups.
- Describe the structure and properties of liquid crystalline phases and how these relate to their materials applications.
- Discuss the effect of molecular weight and dispersity on synthetic polymers and how these are quantified.

- Relate the conformation and viscosity of polymers in solution and the melt to their molecular weight.
- Discuss the properties of amorphous and crystalline polymers.

5. Quantum Chemistry (5 h, CZ, Chapter 12 of the textbook)

Students will understand that:

- Wien's Law states that $T\lambda_{max}$ = constant; the Stefan-Boltzmann law states that the emission of a black body is proportional to T^4. Planck proposed that *electromagnetic oscillators* of frequency ν could acquire or discard energy in quanta of magnitude $h\nu$. Einstein proposed that *atoms* oscillating in a solid with frequency ν could acquire or discard energy in quanta of magnitude $h\nu$.
- The photoelectric effect is the ejection of electrons when radiation of greater than the threshold frequency is incident on a metal; the kinetic energy of the ejected electrons and frequency of the incident radiation are related by $E_k = h\nu\phi$ where ϕ is the work function of the metal. The de Broglie relation for the wavelength, λ, of a particle of linear momentum *p* is $\lambda = \eta/p$.
- A wave function, ψ, contains all the dynamical information about a system and is found by solving the appropriate Schrödinger equation, $-(\bar{h}^2/2m)\mathrm{d}^2\psi/\mathrm{d}x^2 + \mathrm{V}\psi = \mathrm{E}\psi$, subject to constraints on the solutions known as boundary conditions.
- According to the Born interpretation, the probability of finding a particle in a small region of space of volume δV is proportional to $\psi^2\,\delta$V, where ψ is the value of the wave function in the region.
- According to the Heisenberg uncertainty principle, it is impossible to specify simultaneously, with arbitrary precision, both the momentum and position of a particle.
- The energy levels of a particle of mass *m* in a 1-D box of length *L* are $E_n = n^2h^2/8mL^2$, with n = 1, 2,… and the wave functions are $\psi_n(x) = (2/L)^{1/2}\sin(n\pi x/L)$.
- The energy levels of a particle of mass m in a 3-D box of length *L* are $E_n = (n_1^2/L_1^2 + n_2^2/L_2^2 + n_3^2/L_3^2)(h^2/8m)$, with n = 1, 2,… and the wave functions are $\psi_n(x) = (2/L)^{1/2}\sin(n\pi x/L)$.
- Because wave functions do not decay abruptly to zero, particles may tunnel into classically forbidden regions. Two aspects of tunneling include radioactivity and scanning tunneling microscopy.
- The energy levels of a particle of mass m on a circular ring of radius r are $E_{m_I} = m_I^2\hbar^2/2I$ where *I* is the moment of inertia, $I = mr^2$ and $m_I = 0, \pm1, \pm2$, etc.
- The angular momentum of a particle on a ring is quantized and confined to the values $J_z = m_I\hbar$, $m_I = 0, \pm1, \pm2$, etc.
- A particle undergoes harmonic motion if it is subjected to a Hooke's-law restoring force and has a parabolic potential energy, $V(x) = 1/2kx^2$.
- The energy levels of a harmonic oscillator are $E_\nu = (v + ½)h\omega$, where $\omega = (1/2\pi)(k/m)^{1/2}$ and v = 0, 1, 2,…

Related practicals are included in the laboratory-based Module CH334 - Experimental Chemistry II (see description of the CH334 Module for details).

CH334 - Experimental Chemistry II

Instructors: Prof. Henry Curran (Co-Coordinator/Physical Chemistry Practicals), Dr Luca Ronconi (Co-Coordinator/Inorganic Chemistry Practicals), Dr David Cheung, Dr Pau Farras, Prof Donal Leech, Dr Constantina Papatriantafyllopoulou, Dr Chong-Wen Zhou

COURSE OUTLINE WITH LEARNING OUTCOMES (LO)

The *CH334 - Experimental Chemistry II* laboratory-based Module complements the 3rd year *CH307 - Inorganic Chemistry* and *CH313 - Physical Chemistry* lecture-based Modules, which students must also take as a pre-requisite to attend the object practical course.

This course will involve the carrying out of experiments in areas such as inorganic syntheses, analysis and spectroscopic characterization of coordination compounds, correlation of the reactivity and aqueous chemistry of selected transition metal ions with their oxidation states, spectroscopy, electrochemistry, and soft matter chemistry.

Attendance to **all** laboratory sessions is **mandatory**.

On successful completion of this Module, the learner will be able to:

1. set up and carry out selected syntheses aimed at the generation coordination compounds;
2. relate laboratory results to the properties (*e.g.* oxidation states, structures, reactivity) of selected transition metals and their coordination compounds, covered in the associated inorganic chemistry lectures;
3. demonstrate competence in the spectroscopic characterization (*e.g.* IR, UV-Vis spectroscopy) of coordination compounds;
4. demonstrate competence in stoichiometric calculations;
5. set up and perform tests to verify fundamental physical chemistry theories in the laboratory;
6. relate experimental results to the physico-chemical principles dealt with in the associated physical chemistry lectures;
7. recognize the scientific method of planning, developing, conducting and reporting experiments to a scientifically acceptable standard;
8. apply important synthetic and analytical techniques relevant to the professional practice of chemistry;
9. implement safe work practices in a chemistry laboratory, to include awareness of common hazards and appropriate safety precautions.

MODULE DELIVERY

The Module is delivered in 11 practical sessions of 3 hours each (1 practical per week) split into two blocks:

- Inorganic practicals: weeks 1-5 (5 practicals), individual ten-minute oral examination in week 6;
- Physical practicals: weeks 7-12 (6 practicals), individual oral examinations in week 12 during the last practical session.

Specifically, the following practical experiments will be carried out.

1. Inorganic Chemistry

- Investigation of the Oxidation States of Vanadium
- Oxidation of Ethanol by Chromium(VI)
- Synthesis and Characterization of Acetylacetonate Derivatives of Vanadium(IV)
- Investigation of the Aqueous Chemistry of Fe(III), Fe(II), Cu(II) and Ag(I)
- The Cycle of Copper

2. Physical Chemistry

- Rotational-Vibrational Spectrum of HCl
- Beer-Lambert Law
- Polymer Viscosity
- Determination of the Critical Micelle Concentration
- Nernst Equation
- Cyclic Voltammetry of the Ferrocyanide/Ferricyanide Redox Couple

To derive full benefit from the course students should read details of the experiments to be performed **prior to attending the laboratory** and refer to the **literature resources** indicated in the laboratory manual.

TEXTBOOK AND REFERENCE MATERIAL

- Experimental Chemistry II Laboratory Manual 2024 - 2025
- Lecture notes, slides and literature papers provided in due course on Canvas

CH3103 - Validation in the Pharmaceutical and Medical Devices Industry

Instructors: Dr. Constantina Papatriantafyllopoulou (Coordinator), TBA

MODULE DELIVERY AND ASSESSMENT

The Module is delivered in 15 lectures (normally 3 one-hour lectures per week) and 1 two-hour practical.

The Module is assessed through a formal written examination at the end of Semester II (worth 65%) and Continuous Assessment (Project to be undertaken along with a presentation, worth 35%).

Attendance to lectures and the practical session is **mandatory**.

COURSE OUTLINE WITH LEARNING OUTCOMES

This module will cover relevant topics concerning validatory requirements within the (bio)pharmaceutical and chemical industries. Detailed insights into the inner workings of industry are also given.

On successful completion of this Module, the learner will:

- Be introduced to the concept of Validation and its role in the pharmaceutical industry; the Validation Masterplan (VMP) will then be discussed and its benefits outlined.
- Be introduced to the concept of Good Manufacturing Practice (GMP) and Good Laboratory Practice (GLP) in relation to the pharmaceutical and chemical industries.
- Learn of the numerous and pertinent aspects of Cleaning Validation with respect to the manufacturing industry.
- Apply the basic concepts of the course in a laboratory exercise.
- Be provided with a broad knowledge of the subject of Equipment qualification including Design, Installation, Process and Performance Qualification).
- Be introduced to the cutting-edge field of Process Analytical Technology (PAT) and understand its fundamental relevance to the future of pharmaceutical manufacturing.
- Be introduced to Medical Devices and will glean knowledge in the practical aspects of Quality Control, Good Manufacturing Practices and Drug Development in relation to the Medical Device Industry.

CH4106 - Work Placement

GENERAL INFORMATION

The Work Placement is a core part of the BSc Biopharmaceutical Chemistry. Students complete a six-month placement relevant to the programme, which is worth 25% of the Year 4 mark.

All placements must be approved by the School of Chemistry and the Career Development Centre.

Students prepare for the work placement by making use of the supports provided. These include advisory sessions (CV preparation, interview training, etc.) with the Career Development Centre (Tom Fitzgerald) and the placement Coordinator (Prof. Peter Crowley).

Students must comply with University of Galway and Employer agreements for the acceptance of job offers.

Students are required to accept the first work placement offer that they receive and to withdraw from other applications.

Students should be clear on what they are expected to achieve in the placement. In addition to *Technical Skills* the students will develop *People Skills* and *Self Reliance Skills*.

In preparing for placements, students should become familiar with the host organizations, through web searches, company literature, personal contacts, etc. It can be helpful to get advice from students who have returned from, or are currently on, placement.

Students should take care of specific requirements such as travel, accommodation, bank accounts, insurance, etc.

Students who do not prepare appropriately (see Rules and Regulations below) will not be allowed to do a work placement.

Students who have to repeat examinations (15 credits or more) will not be allowed to complete the work placement. Students who pass the Year 3 repeats will do the "on campus" placement.

Prior to the placement students should:

- get familiar with the Learning Outcomes and assessment (see below);
- fully engage with the application and preparation process and comply with rules and regulations;
- prepare appropriately for the specific placement.

GUIDELINES FOR WRITING THE WORK PLACEMENT REPORT

In the final report the student addresses each of the following topics to demonstrate their achievement of the Learning Outcomes.

1. **Job Description.** Include the job description as outlined by the employer/supervisor (max 1 page).
2. **Organization.** Describe the host organization, the main activities and objectives. Describe its management structure and the environment in which it operates its daily business (max 1 page).
3. **Role of Student.** Describe the role you played in the organization (max 1 page).
4. **Technical and General Skills.** List the *Technical Skills*, *People Skills* and *Self Reliance Skills* that were required for the work placement. Describe how these skills were acquired and developed (max 2 pages).
5. **Scientific Knowledge.** Detail the (bio)chemistry and/or pharmacology of the products, analysis and services provided by the company (max 2-3 pages).
6. **Safety Risk Assessment.** Provide a project-specific Health & Safety Risk Assessment (max 1 page).
7. **Relationship to Programme of Study.** Describe how the placement related to your study (max 1 page).
8. **Employability.** Describe the career options that the placement has opened up for you (max 1 page).
9. **CV.** Include your updated CV with a focus on new career possibilities (max 2 pages).
10. **Appendix (optional).** Certificates of skills/achievements, and training completion documents.

Work Placement Agreement

The following Rules and Regulations are strictly enforced to ensure the smooth running of the placement and to ensure that all students are given every opportunity to complete the placement.

BPC STUDENTS ARE OBLIGED TO REVIEW, SIGN AND SUBMIT THIS AGREEMENT.

General

- Register on your course of study to gain access to the Placement Application system.
- Complete and submit on time all placement documentation that is required.
- Activate voicemail on your phone and include a professional voicemail message.
- Ensure that your University of Galway e-mail inbox can receive new messages from the Careers Development System, the Placement Application System, and the placement Coordinator.
- Do not contact any other company regarding placements when you have already obtained a placement.
- Check the Placement Application System and University of Galway e-mail daily for interview schedule updates and to review new job postings.
- Attend all placement related information sessions, presentations, and workshops.
- Conduct yourself professionally in all dealings with employers.

Placement Application Phase

- Apply for as many placements as possible.
- Students can be selected for interview even if they have not applied for the particular placement position.
- Application for a particular placement position is not possible when the closing date has passed.

Placement Interview Phase

- "Confirm interview" on the Placement Application system when selected for interview.
- Research the company prior to interview, *e.g.*, view the company website or speak with a previous intern or student who has had placement there.
- Attend all arranged interviews.
- Present for interview in appropriate business attire.
- Avoid the use of inappropriate language during interviews.
- Be polite and courteous to interviewers at all times.
- Refrain from chewing gum during interviews.
- Demonstrate interest and enthusiasm at the interview. Students who are found to deliberately not perform at interview will be eliminated from the placement process.
- If unable to attend interview due to illness, you are required to submit a medical certificate to the CDC.
- When a company makes an offer you are obliged to accept it. You cannot reject an offer.
- If you are offered two positions on the same day, you can choose your preference.
- You are not permitted to reject an offer and then source your own placement.
- You are not permitted to interview with another company once you have been offered a placement.
- The placement offer you receive is for the duration of the placement period.
- Contact the company immediately and provide any extra information (*e.g.* medical) in a timely manner.

I UNDERSTAND AND ACCEPT THE RULES AND REGULATIONS REGARDING PLACEMENT.

Student Name (in BLOCK LETTERS): _____ Student ID: _____

Course of Study: _____

Student Signature: _____ Date _____