APPROVED

PHAR S8006: Biopharmaceutical Processing (Upstream)

Module Details

Module Code:	PHAR S8006
Full Title:	Biopharmaceutical Processing (Upstream) APPROVED
Valid From::	Semester 2 - 2018/19 (February 2019)
Language of Instruction:	English
Duration:	1 Semester
Credits::	7.5
Module Owner::	Ronan Bree
Departments:	Unknown
Module Description:	The aim of this module is to provide the students with an in-depth knowledge of the upstream processing of biopharmaceuticals (both theoretical and practical topics pertaining to the development, sourcing and production of biopharmaceuticals).

Module Learning Outcome	
On successful completion of this module the learner will be able to:	
#	**Module Learning Outcome Description**
MLO1	Choose appropriate host/vector systems and transfection technologies required for the production of particular recombinant proteins.
MLO2	Design facility lay-outs including details on the practices, equipment and materials required for the upstream processing of biopharmaceuticals.
MLO3	Evaluate how plasmid vectors can be generated/modified in vitro to facilitate high, and sustainable, production levels of recombinant biopharmaceuticals.
MLO4	Synthesise both the apoptosis process and approaches for its detection using online and offline methodologies.
MLO5	Create solutions to overcome the problems associated with bioreactor up-scaling.
MLO6	Apply practical competence in selected molecular and cell culture related techniques.

Pre-requisite learning
Module Recommendations *This is prior learning (or a practical skill) that is strongly recommended before enrolment in this module. You may enrol in this module if you have not acquired the recommended learning but you will have considerable difficulty in passing (i.e. achieving the learning outcomes of) the module. While the prior learning is expressed as named DkIT module(s) it also allows for learning (in another module or modules) which is equivalent to the learning specified in the named module(s).*
No recommendations listed

Module Indicative Content
COURSE CONTENT n/a
A review of recombinant product generation and the industry Detailed overview of gene requirements for expression of a recombinant gene, e.g. promotor, enhancer, selection, suppression, on/off on demand expression etc. Genetic manipulation of cells; expression vectors, transfection, selection, cloning, and characterisation. Recombinant E. coli and other recombinant prokaryotic systems. Yeast and fungal cell culture systems. Recombinant mammalian cell lines and hybridoma cell lines. Chinese Hamster Ovary (CHO) cells as expression systems. CHO genomics. Impact of temperature shifts and microRNAs on the CHO proteome. The arrival of biosimilar production and the challenges ahead for the blockbuster-drug producing companies.
Cell-culture facility design, cell culture & associated practices Considerations for design of a cell culture facility incorporating equipment and protocols. Understand the generation and maintenance of master cell banks, and working cell banks; theory, practice and regulations, freezing/thawing cells, maintaining a cell line, characterisation of cells, sub-culture of cells, monitoring growth and viability. Growth media, serum-free media, media development will also be discussed. Types of culture systems: attached cells (cell factories, roller bottles, hollow fibre bioreactors), suspension cells (stirred tank, airlift and wave bioreactors) and hybrid systems. Single use/disposable bioreactors. Problems of scale up from laboratory to pilot plant to industrial scale, comparability and the use of small-scale models. Fed batch vs Perfusion/Continuous culturing. Cleaning and carryover calculations. Cleaning Validation.
Bioprocess practices Process design/Flowchart overivew of upstream bioprocess. Cell metabolism and process monitoring, Warburg effect. Viral contamination of biprocessing facilities; Viral clearance and strategies to mitigate risk; Gassing strategies in bioreactors (Kla); real-time release testing in biopharmaceutical manufacturing. Process validation lifecycle approach and ongoing process verification; Lab models vs commercial considerations.
Post-translational modifications Regulation of post-translational modifications of recombinant proteins and metabolic engineering to control glycosylation with a focus on fucosylation prevention of monoclonal antibodies. C-terminal lysine and clinical relevance.
Apoptosis overview, its detection and its prevention in cultures. An overview of Apoptosis, with a view to extending the life cycle of cells in a batch environment to increase protein production. The use of online probes and offline techniques to detect apoposis will be discussed.
Advanced Molecular Biology approaches & recent trends Targeted gene integration, gene knock-out and knock in approaches; small interfering RNA (siRNA) and short hairpin RNA (shRNA), various omics technologies; Dihydrofolate reductase based gene amplification and its advantages in recombinant gene expression, applications of restriction enzymes in building recombinant cell lines, ligations, transformations, transfection technologies. Methods to combat 'the position effect' to increase product titre (for example plasmid insertion elements such as S/MARs, Barrier elements, insulators sequences etc. in addition to various gene targeting methods).
LEARNING & TEACHING RESOURCES n/a
Format of Lecture series Lecture delivery will comprise a range of methodology including on-line movie animations, visual demonstrations, large diagrams for illustration purposes as well as information and slide handouts. Novel methods using smartphone web/app based quizzes will also be utilised. Course material and revision quizzes will be made readily available on a virtual learning environment (VLE) for student access. The combination of these methods will facilitate in re-enforcing the student's understanding of some of the technical and mechanistic processes involved. Various aligned classroom assessment techniques will also be employed. These will sometimes include the background knowledge probe, the one minute paper, small group interaction and discussion, question & answer sessions, team presentations to class colleagues, pop-quizzes and open ended questioning. Access to course textbooks will be provided through the DkIT eBook service, which will allow students 24/7 access to suitable reading material. A range of self-assessment, self-reflection and peer learning exercises will be built in to deliveries of both lectures and practical sessions. Relevant publications in the field that complement the course will also be provided to the students. These will inform class discussions throughout the module.
Weekly Practical Sessions Students will attend weekly practical sessions during the module to improve their practical knowledge and skill set. These practicals build on the laboratory experience gained over the previous three years of the students' time in college. In these sessions, topics will be delivered using various approaches, e.g., use of pre-practical videos combined with smartphone based quizzes, digital feedback approaches, delivery via instructor led 'dry' lab practical sessions covering theoretical examples/overviews/audiovisual content/demonstrations showing techniques in detail, via practical sessions at the National Institute for Bioprocessing Research and Training (NIBRT) at UCD in addition to 'wet' lab practical sessions in DkIT. Using instructor led demonstrations /audiovisual content/formative exercises, students will be gain an overview of the details in involved in growing, splitting, waking & freezing cells in culture in addition to aseptic technique and cell culture etiquette. Students will also learn about adherent vs suspension cells, media components, monitoring cell growth, generating master and working cell banks, reducing risks of contamination, detecting contamination (e.g. mycoplasma detection using PCR). As an exercise, students will design a cell culture facility, providing explanations for the layout design and the equipment included. In the DkIT 'wet' labs of the module, students will use antibodies to detect presence/absence of proteins in cell samples using ELISAs, use PCR as a detection tool to test for the presence/absence of specific target sequences in samples, build plasmids through ligations to contain a gene of interest and perform blue/white screening in E.coli to ensure gene of interest is cloned correctly (this builds the student's knowledge of plasmid generation ahead of our lecture series on transfection technology). At the NIBRT facility, students will perform two practical sessions. In session 1, students will thaw a vial of suspension Chinese Hamster Ovary (CHO) cells and inoculate shake flasks; perform a routine passage of cells using aseptic technique; count cells using automatic and manual methods; analyse CHO cell culture using Nova bioprofiler; analyse cells after trypan blue staining. In session 2 at NIBRT, students will either work with a disposable bioreactor or will set-up a 150L Bioreactor for SIP as follows - includes removing sprayballs, changing sparger, put elbows in place, calibrate probes etc; students will identify SIP protocol using P&ID; run pressure test and SIP of the 150L bioreactor; disassemble SIP equipment and prepare bioreactor for CIP by fitting spray balls etc. Where possible, a site-visit to a local industry plant is also performed/or guest speakers will be invited to DkIT. A video-based project is also performed to improve teamwork, communication skills while also stimulating creativity.
Video Project (Technology enhanced learning) Students will work in teams of three and will have one week to record a digital high-definition 2-4 minute video explaining a scientific topic of relevance to a general audience. Its design engages the students with teamwork, brain storming, creativity, technology and also improves their science communication skills.
Virtual Learning Environment (VLE) All lecture notes will be provided to the students through a VLE. This VLE will also be used for access to helpful YouTube video clips and peer reviewed publications of interest to the course. Students will have 24/7 access to the VLE allowing them to download and study at their own pace and in their own time. Screencast and Podcast tutorials will also be made available to the students to download and listen to in their own time. This will facilitate learning and understanding for all students, but in particular the international students who may not have English as their first language.
Formative Assessments Throughout the semester, students will be provided with formative assessments both in lectures and in laboratory environments. These are designed to facilitate group work in problem solving situations. These assessments are built in to the lecture and practical components.
Keeping up-to-date with the Biopharmaceutical industry Break throughs in the Biopharmaceutical field will be sent to the students on a regular basis. This will involve novel developments in the field in addition to postings on jobs/careers in the industry. This concept facilitates the students in preparing for life after college in the Biopharm industry.
ASSESSMENT STRATEGY n/a
Continuous Assessment/Practicals Students will participate in weekly laboratory-based practical sessions as outlined above. Students will perform formal written lab reports/practical class tests in addition to various formative skill tests throughout the module to improve their communication and practical abilities. During the module, the students will spend one day at the National Institute for Bioprocessing Research and Training (NIBRT) at University College Dublin. This day will expose the students to biopharmaceutical plant equipment and systems involved in Upstream Processing. Formative assessments will be performed during the practical sessions which will centre around group work and peer assisted learning. The summative practical assessments will be joined by a summative video project assessment. Students will work in teams of three and will have one week to record a digital high-definition 2-4 minute video clip explaining a scientific topic of relevance to a general audience. Its design engages the students with teamwork, brain storming, creativity, technology and also improves their science communication skills.

Module Assessment

Assessment Breakdown	%
Practical	40.00%
Final Examination	60.00%

Module Special Regulation

Assessments

Full Time On Campus

No Course Work

No Project

Practical

Assessment Type	Practical/Skills Evaluation	**% of Total Mark**	40
Marks Out Of	0	**Pass Mark**	0
Timing	Every Week	**Learning Outcome**	2,3,4,5,6

Duration in minutes	180

Assessment Description
Students will participate in weekly laboratory-based practical sessions in which formative assessments will be performed in interactive group settings (e.g. problem based learning, competency skill-set tests, quizzes, protocol review exercises, worksheet completion etc.). Summative practical assessments will be submitted in addition to a relevant class test and team-based, science/technique based video project.

Final Examination

Assessment Type	Formal Exam	**% of Total Mark**	60
Marks Out Of	0	**Pass Mark**	0
Timing	End-of-Semester	**Learning Outcome**	1,2,3,4,5
Duration in minutes	120		

Assessment Description
End-of-Semester Final Examination

Module Workload

Workload: Full Time On Campus					
Workload Type	*Contact Type*	*Workload Description*	*Frequency*	*Average Weekly Learner Workload*	*Hours*
Lecture	Contact	3 x 1 hour lectures	Every Week	3.00	3
Practical	Contact	1 x 3 hour lab session	Every Week	3.00	3
Directed Reading	Non Contact	Notes / Paper / Textbook reading	Every Week	2.00	2
Independent Study	Non Contact	Self / group study	Every Week	5.00	5
				Total Weekly Learner Workload	13.00
				Total Weekly Contact Hours	6.00

This module has no Part Time On Campus workload.

Module Resources

Recommended Book Resources

Michael Butler. (2007), Cell Culture and Upstream Processing, Taylor and Francis Group, Available on the DkIT NetLibrary collection.

Shijie Liu. (2016), Bioprocess Engineering : Kinetics, Biosystems, Sustainability, and Reactor Design, 2. Elsevier.

Walsh, G.. (2013), Biopharmaceuticals: Biochemistry and biotechnology, 2nd. J. Wiley and Sons.

John M. Davis. (2011), Animal Cell Culture: Essential Methods, 1. Wiley.

Butler, M.. (2004), Animal cell technology, 2nd. BIOS Scientific,.

William Whyte. (2010), Cleanroom Technology: Fundamentals of Design, Testing and Operation, 2nd. Wiley.

John R. W. Masters. (2000), Animal Cell Culture: A Practical Approach, 3. Oxford University Press.

Roshni L. Dutton and Jeno M. Scharer. (2007), Advanced technologies in biopharmaceutical processing, 1. Blackwell Pub.

Glyn Stacey And John Davis. (2007), Medicines from animal cell culture, Wiley.

Pauline M. Doran. (2012), Bioprocess Engineering Principles, 2. Academic Press.

Supplementary Book Resources

Stefan Behme. (2015), Manufacturing of Pharmaceutical Proteins, 2nd. Wiley.

Gerd Gellissen. (2006), Production of recombinant proteins : novel microbial and eukaryotic expression systems, Wiley.

Ganapathy Subramanian. (2012), Biopharmaceutical Production Technology, Wiley.

Elmar Heinzle, Arno P. Biwer, Charles L. Cooney.. (2007), Development of sustainable bioprocesses : modeling and assessment, Wiley.

Sadettin Ozturk & Wei-Shou Hu. (2006), Cell Culture Technology for Pharmaceutical and Cell-Based Therapies (Biotechnology and Bioprocessing), Taylor and Francis Group.

R. Ian Freshney. (2011), Culture of Animal Cells: A Manual of Basic Technique and Specialized Applications, 6. Wiley-Blackwell.

This module does not have any article/paper resources

Other Resources

Textbook collection online with DkIT, 'Access online textbooks through DkIT's eBook collection (go to DkiT library site to begin)'.

website, Biopharm International, http://www.biopharminternational.com/

website, Science Break-throughs: www.breebio.com.

website, American tissue culture collection http://www.atcc.com.

website, European Directorate for the Quality of Medicines and Healthcare http://www.edqm.eu.

website, European Medicines Agency http://www.ema.europa.eu/ema/.

website, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) http://www.ich.org/.

website, HPRA http://www.hpra.ie/.

website, 'U.S. Food and Drug Administration http://www.fda.gov'.

website, The National Institute for Bioprocessing Research and Training (NIBRT): www.nibrt.ie.

website, Bioconnect Ireland: www.biotechnologyireland.com.