PHAR S8006: Biopharmaceutical Processing (Upstream)

Full Title:	Biopharmaceutical Processing (Upstream)
Module Code:	PHAR S8006
Credits:	7.5
Valid From:	Semester 1 - 2015/16 (September 2015)
Module Delivered in	1 programme(s)
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).

Learning Outcomes:

On successful completion of this module the learner should be able to

1. Choose appropriate host/vector systems and transfection technologies required for the production of particular recombinant proteins.
2. Design facility lay-outs including details on the equipment and materials required for the upstream processing of biopharmaceuticals and associated regulatory compliance issues.
3. Evaluate how plasmid vectors can be generated/modified in vitro to facilitate high, and sustainable, production levels of recombinant biopharmaceuticals.
4. Synthesise the cell cycle and apoptosis processes.
5. Create solutions to overcome the problems associated with bioreactor up-scaling.
6. Apply practical competence in selected molecular and cell culture related techniques.

Module Content & Assessment

Indicative Content
COURSE CONTENT n/a
A review of recombinant product generation 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. Post-translational modifications of recombinant proteins and metabolic engineering to control glycosylation with a focus on fucosylation of monoclonal antibodies. Dihydrofolate reductase based gene amplification and its advantages in recombinant gene expression. The rise of the generic and biosimilar era and the challenges ahead for the blockbuster-drug producing companies.
The CHO world: Chinese Hamster Ovary cells as expression systems CHOs as expression systems. CHO genomics. Impact of temperature shifts and miRNAs on the CHO proteome. Signalling pathways in CHO cells.
Cell-culture facility design, cell culture equipment, establishing a cell line, primary culture, continuous cell lines. Design 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. Problems of scale up from laboratory to pilot plant to industrial scale. Fed batch vs Perfusion/Continuous culturing.
A detailed review of the cell cycle. Cell death, apoptosis and necrosis. A detailed overview of the cell cycle and its checkpoints will be presented. This will be linked to the effect on diseases such as cancer in addition to learning about how cells grow in culture, i.e. cell stages, mitotic index relevance etc. A detailed overview of Apoptosis is presented, with a view to extending the life cycle of cells in a batch environment to increase protein production.
Advanced Molecular Biology approaches Gene targeting, small interfering RNA (siRNA), applications of restriction enzymes in building cell lines, ligations, transformations, transfection technology, gene recombination using recombinases. Methods to combat 'the position effect' to increase product titre (e.g. S/MARs, Barrier elements, insulators sequences placed in plasmids etc. in addition to various gene targeting methods). The use of microRNA in the Biopharm/CHO industry.
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 Classroom Response Systems (CRS) 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 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 eBrary service (access to more than 50,000 multidisciplinary e-books), 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.
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., via by 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 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 set-up a 150L Bioreactor for SIP - 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.

Indicative Content
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. The video is submitted as part of the CA component of the module. 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 possess fluent English.
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 Students will participate in weekly laboratory-based practical sessions as outlined above. Students will perform formal written lab reports 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 pharmaceutical 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 laboratory reports 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. The video is submitted as part of the CA component of the module. It's design engages the students with teamwork, brain storming, creativity, technology and also improves their science communication skills.

Assessment Breakdown	%
Course Work	40.00%
End of Module Formal Examination	60.00%

Full Time

Course Work							
Assessment Type	*Assessment Description*	*Outcome addressed*	*% of total*	*Marks Out Of*	*Pass Marks*	*Assessment Date*	*Duration*
Practical/Skills Evaluation	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, quizzes, protocol review exercises, worksheet completion etc.). Summative practical laboratory reports will be submitted in addition to a team-based, science video project.	2,3,4,5,6	40.00	0	0	Every Week	0

No Project

No Practical

End of Module Formal Examination							
Assessment Type	*Assessment Description*	*Outcome addressed*	*% of total*	*Marks Out Of*	*Pass Marks*	*Assessment Date*	*Duration*
Formal Exam	End-of-Semester Final Examination	1,2,3,4,5	60.00	0	0	End-of-Semester	0

Reassessment Requirement
A repeat examination *Reassessment of this module will consist of a repeat examination. It is possible that there will also be a requirement to be reassessed in a coursework element.*

DKIT reserves the right to alter the nature and timings of assessment

Module Workload & Resources

Workload: Full Time

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

This course has no Part Time workload.

Resources

Recommended Book Resources

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

Shijie Liu 2012, *Bioprocess Engineering : Kinetics, Biosystems, Sustainability, and Reactor Design*, 1 Ed., Elsevier available online with DkIT - Dawsonera collection

Walsh, G. 2003, *Biopharmaceuticals: Biochemistry and biotechnology*, 2nd Ed., J. Wiley and Sons

John M. Davis 2011, *Animal Cell Culture: Essential Methods*, 1 Ed., Wiley available online with DkIT - Dawsonera collection

Butler, M. 2004, *Animal cell technology*, 2nd Ed., BIOS Scientific, available online with DkIT - Dawsonera collection

William Whyte 2010, *Cleanroom Technology: Fundamentals of Design, Testing and Operation*, 2 Ed., Wiley

John R. W. Masters 2000, *Animal Cell Culture: A Practical Approach*, 3 Ed., Oxford University Press available online with DkIT - Dawsonera collection

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

Glyn Stacey And John Davis 2007, *Medicines from animal cell culture*, Wiley available online with DkIT - Dawsonera collection

Pauline M. Doran 2012, *Bioprocess Engineering Principles*, 2 Ed., Academic Press

Supplementary Book Resources

Resources

Recommended Book Resources

Stefan Behme 2009, *Manufacturing of Pharmaceutical Proteins*, 1 Ed., Wiley available online with DkIT - Dawsonera collection

Gerd Gellissen 2006, *Production of recombinant proteins : novel microbial and eukaryotic expression systems*, Wiley available online with DkIT - Dawsonera collection

Ganapathy Subramanian 2012, *Biopharmaceutical Production Technology*, Wiley available online with DkIT - Dawsonera collection

Elmar Heinzle, Arno P. Biwer, Charles L. Cooney. 2007, *Development of sustainable bioprocesses : modeling and assessment*, Wiley available online with DkIT - Dawsonera collection

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 2010, *Culture of Animal Cells: A Manual of Basic Technique and Specialized Applications*, 6 Ed., Wiley-Blackwell

This module does not have any article/paper resources

Other Resources

Textbook collection online with DkIT: *'Access online textbooks through DkIT's dawsonera and eBrary collection (go to DkiT library site to begin)'*

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: *Irish Medical Board http://www.imb.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: *Biotechnology Ireland www.biotechnologyireland.com*

Link: *Library Catalogue*
http://tinyurl.com/pbfmh8a

Link: *Library Catalogue*
http://tinyurl.com/kzs953f

Module Delivered in

Programme Code	Programme	Semester	Delivery
DK_SBIOP_8	Bachelor of Science (Honours) in Biopharmaceutical Science	1	Mandatory