Biopharmaceutical Technology

Syllabus of the theory papers

BPT1: BIOPHARMACEUTICAL PROCESS ENGINEERING

Total hours:52

Unit-1 **10 hours**

Mass Balances and Energy Balances

Physical variables, dimensions and units, dimensional analysis, laws of conservation of mass, mass balances with and without reactions, unsteady steady state mass balances. Thermodynamic principles, laws of thermodynamics in bioprocess context, general energy balances for bioprocess systems, energy balances calculations without reactions and due to reactions, heat of reaction of process with biomass production, unsteady steady state energy balances.

Unit-2 **08 hours**

Engineering of Bioreactions and Bioreactors

Overview of biological reactions and bioproducts, reaction theory, reaction kinetics of biological systems- Yields in cell culture, cell growth kinetics, heterogenous reaction systems in bioprocess. Purpose and importance of bioreactors in bioprocess industries, requirements for a bioreactor, development of bioreactors, classification of bioreactors, elements in bioreactor design, major components of bioreactor and their purpose, bioreactor configurations.

Unit-3 **08 hours**

Fluid Flow and Mixing

Rheological properties of fermentation broths, factors affecting broth viscosity, functions of mixing, mixing equipment, flow patterns in stirred tank, impellers, stirrer power requirements, power input by gassing, impeller pumping capacity, suspension of solids, mechanism of mixing, assessing mixing effectiveness, scale up of mixing systems, improve mixing in bioreactors, multiple impellers, retrofitting effect of rheological properties on mixing, roleof shear in stirred bioreactors.

Unit-4 **10 hours**

Heat and Mass Transfer

Mechanism of heat transfer, heat transfer between fluids, design equations for heat transfer systems, applications of design equations, hydrodynamic considerations with cooling coils, heat transfer in agitated tank and columns. Gas-liquid mass transfer in bioprocessing: role of

diffusion in bioprocessing, film theory, convective mass transfer, oxygen uptake in cell cultures-factors affecting oxygen transfer in bioreactors, measuring dissolved oxygen concentration-measurement of k_{La}, measurement of specific oxygen uptake rate

Unit-5 **08 hours**

Unit Operations

Air conditioning and humidification, drying, solid-liquid extraction, crystallization, evaporation, distillation, filtration, size, reduction, solid dosage forms.

Unit-6 **08 hours**

Process Control and Optimisation

Fundamentals of process control, control strategies, multivariable and supervisory control, scale up and optimisation, modelling and assessment in process development, process and fermentation models for development of bioprocesses for biopharmaceuticals, sustainability assessment of bioprocess. Process economics of bioproducts.

Reference Books:

1.Anthony J. Hickey, David Ganderton (2009) Pharmaceutical Process Engineering, 2nd Edition, CRC Press.

2.David J. am Ende (2010) Chemical Engineering in the Pharmaceutical Industry: R&D to Manufacturing. John Wiley & Sons, Inc.

3.Michael L. Shuler, Fikret Kargi (2017) Bioprocess Engineering: Basic Concepts, 3rd Edition, Pearson publishers.

4.Douglas S. Clark, Harvey W. Blanch (1997) Biochemical Engineering, 2nd Edition, CRC press.

5. Pauline M. Doran (2013) Bioprocess Engineering Principles, 2nd Edition, Academic Press.

BPT2: BIOTHERAPEUTICS AND BIOLOGICS

Total hours:52

Unit-1 **10 hours**

Introduction to Biopharmaceuticals and Biogenerics

Introduction to Biopharmaceuticals and pharmaceutical biotechnology, Biopharmaceuticals: current status and future prospects, generic and branded biopharmaceuticals, overview of life history for development of biopharmaceuticals. Discovery of protein or peptide based therapeutics: In-silico, pharmaco-informatics. Pre-clinical toxicity assessment, Clinical trial phases and design, clinical data management, concept of Pharmacovigilance.

Unit-2 **8 hours**

Impact of omics in Drug Discovery

Pharmacogenetics, Pharmacogenomics and proteomics, structural, functional and comparative genomics, DNA & oligonucleotides microarrays, genetically engineered animals, Integration of personalized and systems medicines, pharmacogenomics in preclinical and clinical development of drugs

Unit-3 **8 hours**

Pharmacokinetics and Pharmacodynamics of Biopharmaceuticals

Definition, rationales, absorption, distribution and metabolism pathway. Factors governing absorption of drug. Pharmacokinetics and Pharmacodynamics of therapeutic peptides. Dose response relationship, interspecies scaling, heterogeneity of therapeutic proteins.Chemical modification of therapeutic proteins

Unit-4 **10 hours**

Immunotherapeutic & Immunodiagnostics

Overview of antibody based therapeutics, biologics for autoimmunity and inflammation, vaccine- adjuvant technology, genetically engineered vaccines, cancer vaccines, present and future biologics. Principles of immunodiagnostic assay based on solid phase system: Malarial & HIV diagnostic kits as case study. Fluorescent ligands and radio-isotope tracers, principles and instrumentation for molecular diagnostics (Time resolved fluorescence immunoassay, light scattering principles), PCR and nucleic acid based diagnostics, imaging techniques.

Unit-5 **8 hours**

Biopharmaceuticals Based Delivery Systems

Novel drug delivery systems for biopharmaceuticals (rate controlled and site specific), Nanotechnology based miniaturization of biopharmaceuticals and therapeutics, peptides for

intracellular targeting, delivery of nucleic acids and therapeutic peptides, concept of responsive or smart drug delivery system.

Unit-6 **8 hours**

Formulation of Biopharmaceuticals

Rational for formulation of biotherapeutics, formulation recipients: solubility enhancers, anti aggregating agents, buffers, cryoprotectants, antioxidants and preservatives etc significance with relevant examples. Methods to enhance shelf life protein based therapeutics. Packaging techniques and quality analysis of product.

Reference Books:

1.Gary Walsh (2003) Biopharmaceuticals: Biochemistry and Biotechnology, 2nd Edition, John Wiley & Sons, Inc.

2.Daan J A Crommelin (2010), Pharmaceutical Biotechnology, 2nd Edition, Taylor & Francis Group.

3.Rodney J. Y. Ho (2013) Biotechnology and Biopharmaceuticals: Transforming Proteins and Genes into Drugs, 2ndEdition, John Wiley & Sons, Inc.

4.Gary Walsh (2007) Pharmaceutical Biotechnology: Concepts and Applications. John Wiley & Sons, Inc.

5.Oliver Kayser, Heribert Warzecha (2012) Pharmaceutical Biotechnology: Drug Discovery and Clinical Applications, 2nd Edition. John Wiley & Sons, Inc.

BPT3: UPSTREAM AND DOWNSTREAM PROCESSING OF BIOPHARMACEUTICALS

Total hours:52

Unit-1 **10 hours**

Industrial cell growth and expression systems

Animal cells suspension culture- types used for large-scale production in suspension culture, aseptic techniques, cell cycle in bioprocess, Cell growth and protein expression kinetics, Cell viability measurement, contamination detection in animal cell culture, expression of recombinant proteins in animal cell culture systems.

Unit-2 **08 hours**

Media, bioreactor design and upstream cGMP operations

Culture media for cell culture, cell culture reactors, operating modes for reactors, Cell culture reactors design and operation, rheological properties of fermentation fluid, oxygen transfer rate determination, sampling and sample handling for process control, perfusion culture system, process optimization, foam control systems, decontamination of bioprocess, inoculum preparation and development, scale up strategies.

Unit-3 **08 hours**

Biopharmaceuticals manufacturing facility design and operations

Facility criteria: Clean room, CDS Process, CIP protocol, production and distribution WFI grade water, sources of biopharmaceuticals, upstream processing biopharmaceuticals (cell banking and preservation, cell based culturing and fermentation process).

Unit-4 **10 hours**

Recovery of cells, protein captures and process development in downstream purification

Cell separation, disruption, flocculation and lysis methods, expanded bed chromatography, surface energetics of biomass disposition, filter aids, protein adsorption systems. Scale down of biopharmaceutical purification operations, adsorption in stimulated moving beds, Bioseparation by magnetic field adsorbents, high throughput technologies of protein purification, purification by self cleaving aggregation tags, LPS removal, depyrogenation methods.

Unit-5 **08 hours**

Biopharmaceuticals process analysis techniques

Basis of biochemical characterization (protein structure, forces, hydration, protein folding), protein stability, blotting methods, electrophoresis (iso-electric focusing, capillary

electrophoresis, 2D electrophoresis etc), bioassays, immuno assay, mass spectroscopy, principles of hybrid spectroscopic method (GC-MS, MS-MS- LC-MS, etc).

Unit-6 **08 hours**

Biopharmaceuticals: Finished product polishing technology

Protein Crystallization, freeze drying of biopharmaceuticals, protein ultra filtration technique, virus retentive filters and finished biopharmaceuticals products bio burden test.

Reference Books:

1. Michael C. Flickinger (2013) Upstream Industrial Biotechnology: Expression systems & process development and equipment, process design, sensing, control, and cGMP operations. John Wiley & Sons, Inc.
2. Michael C. Flickinger (2013) Downstream Industrial Biotechnology. John Wiley & Sons, Inc.
3. Daan J A Crommelin (2013) Pharmaceutical Biotechnology: Fundamentals and Applications. Springer Science and Business Media.

BPT E: Syllabus of the Elective theory papers

(Choose any one from the following)

BPTE1: PRODUCTION/ MANUFACTURING BIOLOGIST

Unit-1 **08 hours**

Supervision of bio pharmaceutical production process

Supervise bio pharmaceutical production activities: Bio pharmaceutical production schedule and guidelines to production operators to handle production activities, Directions for junior biologists/ production operators - proper ingredients, temperatures, pressure and mixing times, etc.

Unit-2 **10 hours**

Documentation and Reporting

Documentation - Documentation of activities in the production process, Record of production output for each shift operation in the Batch Process.

Reporting – Following of approved guidelines of respective Drug Administration Body (MHRA, USFDA, CDSCO, etc.), Standard Operating Procedures and other statutory requirements, Reporting of breakdowns, Maintenance of GMP standards at shop floor and conditions suitable for production of quality products.

Unit-3 **08 hours**

Manage staff and inventory

Staff - Procedures to be followed in Managing staff details at production site. Role of production staff during audit

Inventory - Stock of raw materials and chemicals for production activities, Requirement and source materials as per daily production schedule, labeling, raw material conditions, batch no., shelf life and quantities, etc.

Unit-4 **10 hours**

Maintain a healthy, safe and secure working environment in the life sciences facility

Self monitor and safety principles and standards, behavioural safety of workmen to current Good Manufacturing Practices (cGMP). Shop floor standards. Reporting of health issues, safety and security policies and procedures.

Managing emergency procedures: illness, accidents, fires, evacuation of worker/s during emergency.

Unit-5 **08 hours**

Coordination with Shift Supervisor

Work instructions from reporting supervisor, Reporting to supervisor - process-flow improvements and production defects received from previous process, potential hazards or expected process disruptions, maintenance and repair schedule proactively, handover of completed work.

Unit-6 **08 hours**

Coordination within the team and with cross functional teams

Team player: Working with colleagues and sharing of work, work flow related difficulties.

Interact with colleagues from cross functional teams: Feedback from Quality Control and Quality Assurance, Completion of work on time, support to Quality Assurance team during audits, coordination during breakdowns and for preventive and corrective maintenance, Coordination with Stores.

BPTE2: QUALITY CONTROL/QUALITY ASSURANCE BIOLOGIST

Unit-1 **16 hours**

Essentials of quality control

Preparations - buffer, solvents, solutions and microbial media for running bio-analytical quality tests, assays to carry out quality control procedures on biopharmaceutical products.

Concepts of pharmacopeia like BP, USP, EP and other applicable guidelines such as WHO, ICH and EMEA, etc., statistical tools and software like combistats, safe handling of infectious materials like cultures, strains and seed strains, procedures for handling infectious spillage control, GLP/GMP, biochemical analysis of proteins, bio analytical and microbiological methods, working of instruments/apparatus/equipment, biological assays, application of various analytical techniques such as HPLC, capillary electrophoresis including icIEF, FTIR, Circular Dichroism, UV and Fluorescence spectroscopy, ELISAs, enzyme assays and other applicable methods for the testing of biopharmaceuticals, application of microbiological techniques such as air monitoring, water testing, surface monitoring, microbial monitoring, biosafety levels and biosafety hazards.

Unit-2 **10 hours**

Quality Assurance

Quality checks - quality assurance samples, master sample, internal controls, statistical analysis of test data, techniques and concepts of statistical quality control and statistical process control, non-conformities. Operational aspects – calibration, accuracy checks of quality control equipments like stability chambers and BOD incubators, HPLC, gas chromatography, photoflourometer, etc., application softwares used in quality analysis.

Unit-3 **06 hours**

Safety and Security at workplace

Different types of occupational health hazards, knowledge of chemical substances, characteristics & safety measures, use of safety gears, masks, gloves & accessories, evacuation procedures for workers & visitors. Health, safety & security issues – types (illness, fire accidents), company policies and procedures, When and how to report, summon medical assistance & emergency services.

Unit-4 **06 hours**

Interpersonal Skills

Understand work output requirements, company rules, guidelines & policies related to the process flow, identifying and reporting issues requiring intervention, delivery of quality work on

time & report any anticipated reasons for the delay, importance of team work, resolution of conflicts, multi-tasking, training the team members, knowledge of project management.

Unit-5 **06 hours**

Clean work station

Cleaning the work area and equipments, materials and equipments required for cleaning, adequate ventilation for the work area, personal protective equipments, dealing with accidental damage, procuring and storing housekeeping equipment and supplies, disposal of wastes, maintain schedules and records for housekeeping.

Unit-6 **08 hours**

Reporting and documentation in quality

Reporting – company procedures, escalation matrix for reporting identified issues - defects, problem, incidents, quality issues and test results, feedback to production manager and R&D staff. Documentation – procedures and good documentation practices, offline and online mode, accuracy, details, controlled document files and test records, regulatory and compliance requirements, inspection - procedures, protocols and checklists, inspection reports.

Syllabus of the practical papers

BPTL1: BIOPHARMACEUTICAL TECHNOLOGY LAB

1. Introduction to CDS (cleaning, decontamination and sanitization) protocols as per GLP norms.
2. Sterility testing of finished biopharmaceutical products (Injectables / freeze dried formulations).
3. PCR based optimization and quality control assay.
4. Comet assay: single cell gel electrophoresis.
5. Determination of bacterial endo-toxins.
6. Preparation of blank and loaded liposome for delivery of drug.
7. Preparation and evaluation of controlled release formulation.
8. Anti Lipid Peroxidation assay.
9. Determination of pharmacokinetic (PK) release profile of biopharmaceuticals.
10. Determination of iso-electric (PI) of biopharmaceuticals.
11. Isolation, screening and quantification of bioactive compounds from natural source.
12. Separation and purification of isolated bioactive components.

Reference Books:

1. Gary Walsh (2003) Biopharmaceuticals: Biochemistry and Biotechnology, 2nd Edition. John Wiley & Sons, Inc.
2. Rodney J. Y. Ho (2013) Biotechnology and Biopharmaceuticals: Transforming Proteins and Genes into Drugs, 2nd Edition. John Wiley & Sons, Inc.
3. Gary Walsh (2007) Pharmaceutical Biotechnology: Concepts and Applications. John Wiley & Sons, Inc.
4. Oliver Kayser, Heribert Warzecha (2012) Pharmaceutical Biotechnology: Drug Discovery and Clinical Applications, 2nd Edition. John Wiley & Sons, Inc.

BPTL2: UPSTREAM AND DOWNSTREAM BIOPROCESSING LAB

1. Introduction to GLP guidelines pertaining to upstream and downstream processing.
2. Induction of callus and suspension culture.
3. Monolayer animal cell cultivation and trypsinization method.
4. Development of inoculum: single stage and multistage.
5. Lab scale fermenter design and operational details.
6. Media formulation and sterilization methods for thermo stable and thermo labile media constituents.
7. Determination of doubling time of given culture.
8. Optimization of recovery process: centrifugation, filtration.
9. Determination of polarity / partition coefficient of bio molecule by aqueous two phase method.
10. Protein enrichment operation: salting out, organic solvent.
11. Process design and simulation of biopharmaceuticals production using SuperPro Designer.
12. Design of experiments and optimisation using Design expert.

Reference Books:

1. Michael C. Flickinger (2013) Upstream Industrial Biotechnology: Expression systems & process development and equipment, process design, sensing, control, and cgmp operations. John Wiley & Sons, Inc.
2. Michael C. Flickinger (2013) Downstream Industrial Biotechnology. John Wiley & Sons, Inc.