Studienbrief

USP, DSP & Process Optimization

Modul 3.1

Im Studiengang Biopharmazeutisch-Medizintechnische Wissenschaften

(Master of Science)

Gefördert vom Ministerium für Soziales und Integration Baden-Württemberg aus Mitteln des Europäischen Sozialfonds sowie vom Ministerium für Wissenschaft, Forschung und Kunst Baden-Württemberg

Modulnummer	3.1
Modultitel	USP, DSP & Process Optimization
Leistungspunkte	6 ECTS
Sprache	Englisch
Modulverantwortlicher	Prof. Dr. Antje Labes
Dozenten	Prof. Dr. Antje Labes
Studiengang	Biopharmazeutisch-Medizintechnische Wissenschaften (M.Sc.)
Voraussetzungen (inhaltlich)	Fachwissenschaftliche Grundlagen
Voraussetzungen (formal)	Keine
Lernziele	Das Modul USP, DSP & Process Optimization vermittelt den Studierenden verschiedenen Möglichkeiten der Prozessführung für die Kultivierung von verschiedenen Zellsystemen. Die Studierenden lernen Massenbilanzen für die Prozesse abzuleiten und einfache Vorhersagen bezüglich des Zellwachstums und Substratverbrauchs zu berechnen. Darüber hinaus sind die Studierenden in der Lage kostenrelevante Faktoren zu identifizieren und verschiedenen Aufarbeitungstechniken von pharmazeutischen Proteinen und die relevanten Einflussfaktoren aufzuzählen und zu beschreiben. Die Studierenden sind in der Lage, Risikoanalysen durchzuführen und Prozesse einem strukturierten Optimierungsprozess zu unterziehen.
Inhalte	**Upstream Processing (USP)** - Ökonomische Aspekte der Prozessentwicklung - Bioreaktoren: Mischer und Reaktortypen - Zellwachstum in Bioreaktoren: Kinetik, Massenbilanzen und Prozessführung, Wachstumsmodelle - Bioprozessanalytik und Steuerung: Sensoren, Automatisierung - Transportvorgänge in Biosuspensionen **Downstream Processing (DSP**) - Allgemeine Aspekte der biotechnologischen Aufarbeitung - Prozesschromatographie, chromatographische Parameter, Arten der Chromatographie, - Radialchromatographie, kontinuierliche Chromatographie - Monollithische Säulen, Membranadsorber - Filtration: Dead-End-Filtration, Tangentialflussfiltration, Tiefenfiltration, Membranfiltration - Kristallisation und Aggregation, Zwei-Phasensysteme - Zellaufschlussmethoden - Virussicherheit **Process Optimization** - Prozessüberblick (Prozessdarstellung, Ermittlung der wichtigsten Prozessspezifikationen (CTQs)) - Prozessdarstellungen und Identifikation von Einflussgrößen, Grafische Darstellung von Prozessdaten: Urwertkarte, Medianzyklen-Diagramm,

	Histogramme, Streudiagramme, signifikante und zufällige Unterschiede - Prüfsysteme: Geeignete Messsysteme und Eignungsnachweis von Prüfprozessen (Bias, Wiederholpräzision, Vergleichspräzision, Linearität und Stabilität), systematische Messabweichung, GR&R-Studie - Prozessfähigkeit: cpk-Wert, Prozessfähigkeitsindizes u.ä. nach DIN ISO 21747 - Prozessanalyse: Regressionsanalyse, kurze Einführung/Wiederholung in die statistische Versuchsplanung - Prozessverbesserung: Poke-Yoka-Prinzip, 635-Mehtode, Risikoanalyse mit FMEA und Fehlerbaumanalyse
Literatur	- Bioprozesstechnik, Horst Chmiel, 3. Auflage, Spektrum-Verlag - Bioverfahrensentwicklung, Winfried Storhas, 2. Auflage, Wiley-VCH - Nullfehlermanagement, Johann Wappis und Berndt Jung, 4. Auflage, Hanser-Verlag
Lehrveranstaltungen und Lehrformen	Präsenzveranstaltungen: - Praktikum - Modulprüfung E-Learning - Online-Sprechstunde - Skripte und selbstständige Nachbereitung Summe: 180 h
Prüfungsform	90 Min Klausur Prüfungssprache ist Deutsch.

Bioprocessing or biotechnology is used in the production of pharmaceuticals, foods, flavours, fuels and chemicals with the aid of a biocatalyst such as an enzyme, microorganisms, plant cell, or animal cell in a bioreactor. It also involves genetic engineering for the manipulation of plants, animals, and microorganisms such as yeasts, bacteria and fungi. Downstream processing is required to remove impurities, bulk- volume reduction and simultaneous concentration of the desired product from the bioreactor.

Most pharmaceutical substances are manufactured in batch processes by

(a) chemical synthesis,

(b) fermentation,

(c) isolation and recovery from natural sources, and

(d) a combination of the above.

Fermentation broths are usually very dilute and contain many complex compounds. Hence, a bioprocess is any process that uses complete living cells or their components (e.g., bacteria, enzymes, chloroplast) to obtain desired products. This process is often also referred to as fermentation.

Bioprocesses can be largely classified into three stages: preparation, production and purification. Preparation frequently involves nutrient media and equipment sterilisation, while bioreaction kinetics, oxygen transfer and operational strategy are key to the production stage, as are separation operations to product purification. Central to the successful bioprocess is, however, not only the optimisation of these three stages, but also a biocatalyst which is capable of utilising substrate efficiently and forming the desired product with few or no by-products. Without this, the bioprocess will be constrained, despite the best efforts to maximise the upstream production kinetics and downstream product recovery.

Bioprocessing equipment encompasses a broad spectrum of equipment for specific functions and applications. In broad terms and with respect to a process flow diagram the equipment may be divided in three categories: upstream, downstream, and support. Upstream equipment deals with the growth of a host organism to produce a product. The product may be the organisms themselves, it may be held internal to the organism, or it may be excreted into the growth medium. Purification, for example, filtration, and chromatography of the resulting harvest from the upstream process is handled by downstream equipment. Other pieces of equipment used in biomanufacturing such as incubators, utility carts, liquid mixers, holding tanks, bead mills and other cell disruptors can be defined as support equipment. Accordingly, in process development, a number of different technologies must be integrated and kept for quality control.

Depending on the scientific background, bioprocessing and its stages are differently defined. During this course, we will follow the OECD definition for biotechnology and the structuring of a bioprocess into upstream and downstream accordingly:

Upstream processing which involves preparation of liquid medium, separation of particulate and inhibitory chemicals from the medium, sterilization, air purification etc. Upstream processes include selection of a microbial strain characterized by the ability to synthesize a specific product having the desired commercial value. This strain then is subjected to improvement protocols to maximize the ability of the strain to synthesize

economical amounts of the product. Included in the upstream phase is the fermentation process itself which usually is carried out in large tanks known as fermenters or bioreactors. In addition to mechanical parts which provide proper conditions inside the tank such as aeration, cooling, agitation, etc., the tank is usually also equipped with complex sets of monitors and control devices in order to run the microbial growth and product synthesis under optimized conditions. The processing of the fermentation reactions inside the fermenter can be done using many modifications of engineering technologies. One of the most commonly used fermenter types is the stirred-tank fermenter which utilizes mechanical agitation principles, mainly using radial-flow impellers, during the fermentation process. Fermentation involves the conversion of substrates to desired product with the help of biological agents such as microorganisms.

Downstream processing which involves separation of cells from the fermentation broth, purification and concentration of desired product and waste disposal or recycle. Downstream processing, the various stages that follow the fermentation process, involves suitable techniques and methods for recovery, purification, and characterization of the

desired fermentation product. A vast array of methods for downstream processing, such as centrifugation, filtration, and chromatography, may be applied. These methods vary according to the chemical and physical nature, as well as the desired grade, of the final product.

1.2 Process design, general considerations in bioprocess engineering

Given a product and a desired annual production rate (plant throughput) bioprocess design endeavors to answer the following questions: What are the required amounts of raw materials and utilities? What is the required size of process equipment and supporting utilities? Can the product be produced in an existing facility or a new plant is required? What is the total capital investment? What is the manufacturing cost? What is the optimum batch size? How long does a single batch take? How much product can be generated per year? During the course of a batch what is the demand for various resources (e.g., raw materials, labor, utilities, etc.)? What is the total amount of resources consumed? Which process steps or resources constitute bottlenecks? What changes can increase throughput? What is the environmental impact of the process (i.e., amount and type of waste materials)? Which design is the "best" among several plausible alternatives?

Process design is the conceptual work done prior to building, expanding or retrofitting a process plant. It consists of two main activities, process synthesis and process analysis. Process synthesis is the selection and arrangement of a set of unit operations (process steps) capable of producing the desired product at an acceptable cost and quality. Process analysis is the evaluation and comparison of different process synthesis solutions. In general, a synthesis step is usually followed by an analysis step, and the results of analysis determine the subsequent synthesis step. Process design and project economic evaluation require integration of knowledge from many different scientific and engineering disciplines and are carried out at various levels of detail. Figure XY presents the need for various types of design estimates during the lifecycle of product development and commercialization. The trapezoidal shape of the graph represents the drastic reduction in product candidates as we move from feasibility studies to commercialization. In fact, the chances of

commercialization at the research stage for a new product are only about 1 to 3%, at the development stage they are about 10 to 25%, and at the pilot plant stage they are about 40 to 60%. Order-of-magnitude estimates are usually practiced by experienced engineers who have worked on similar projects in the past. They take minutes or hours to complete but the error in the estimate can be as high as 50%. Most engineers employed by operating companies usually perform level 2 and 3 studies. Such studies take days or weeks to complete using appropriate computer aids. The main objective of such studies is to evaluate alternatives and pinpoint the most cost-sensitive areas – the economic "hot- spots" – of a complex process. The results of such analyses are used to plan future research and development and to generate project budgets. Level 4 and 5 studies are usually performed by engineering and construction companies that are hired to build new plants for promising new products that are at an advanced stage of development. Such estimates are beyond the scope of this chapter. Instead, the focus of the material in the rest of this chapter will be on level 1, 2, and 3 studies. It should also be noted that opportunities for creative process design work are usually limited to preliminary studies. By the time detailed engineering work is initiated, a process is more than 80% fixed. Furthermore, the vast majority of important decisions for capital expenditures and product commercialization are based on results of preliminary process design and cost analysis. This explains why it is so important for a new engineer to master the skills of preliminary process design and cost estimation. Environmental impact assessment is an activity closely related to process design and cost estimation. Biochemical plants generate a wide range of liquid, solid, and gaseous waste streams that require treatment prior to discharge. The cost associated with waste treatment and disposal has skyrocketed in recent years due to increasingly stricter environmental regulations. This cost can be reduced through minimization of waste generation at the source. However, generation of waste from a chemical or biochemical process is dependent upon the

Ansprechpartner

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„Pharmazeutische Grundlagen und Antikörper- Engineering" im Studiengang „Biopharmazeutisch-Medizintechnische Wissenschaften (BM-Wiss)" wurde entwickelt im Projekt Cross-Over, das aus Mitteln des Ministeriums für Wissenschaft, Forschung und Kunst des Landes Baden-Württemberg gefördert und aus dem Europäischen Sozialfonds der Europäischen Union kofinanziert wird (Förderkennzeichen: 696606). Dabei handelt es sich um ein Vorhaben im Programm „Auf- und Ausbau von Strukturen der wissenschaftlichen Weiterbildung an Hochschulen in Baden-Württemberg".