

Upstream Fermentation and Research Laboratory Design, Safety, and Validation

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Abstract — *The fermentation process plays an essential role in biotechnology and biopharmaceutical research, serving as a foundation for the production of various valuable compounds. This abstract provides an overview of recent advancements in fermentation laboratory design and equipment selection aimed at enhancing research efficiency and safety. Key considerations in facility design, including spatial organization, and safety implementations, are discussed in the context of meeting specific research and production needs. Moreover, the importance of equipment selection, ranging from fermenters and bioreactors to ancillary systems, is highlighted, emphasizing factors such as control capabilities and regulatory compliance. Furthermore, the significance of integrating advanced technologies and rigorous operational protocols to drive innovation and scientific discovery in the field of biotechnology and biopharmaceuticals.*

Key Terms — *fermentation, laboratory, safety, validation*

PROBLEM STATEMENT

The design and commissioning of a new upstream fermentation laboratory represent an essential endeavor in the field of biotechnology and biopharmaceutical production. Fermentation processes play a crucial role in the production of various products, including biofuels, pharmaceuticals, enzymes, and food additives. Establishing a well-designed and properly equipped fermentation laboratory is essential for conducting research, developing new products, and optimizing production processes.

Designing a new fermentation laboratory involves careful consideration of various factors, including facility layout, equipment selection, process design, safety protocols, and regulatory

compliance. The goal is to create a conducive environment for conducting fermentation experiments while ensuring safety, efficiency, and compliance with industry standards and regulations.

Commissioning a new fermentation laboratory involves the installation, testing, and validation of equipment and systems to ensure that they meet specified requirements and perform as intended. This process requires close collaboration between engineers, scientists, technicians, and regulatory experts to ensure that the laboratory meets all necessary criteria for operation.

Research Description

The design and commissioning of a new fermentation laboratory require careful planning, coordination, and attention to detail. By considering factors such as facility layout, equipment selection, process design, safety protocols, and regulatory compliance, a well-functioning fermentation laboratory can be established to support research, development, and production activities in the field of biotechnology and biopharmaceuticals.

Research Objectives

The objective of this project is to design and commission a new fermentation laboratory facility that meets the specific needs of biotechnology and biopharmaceutical research and production. This objective encompasses several key goals like facility design, equipment selection, process optimization, safety implementations, commissioning, and validation.

LITERATURE REVIEW

Commissioning and start-up (CSU) are essential stages that must be completed before a facility can commence initial operations and achieve its commercial objectives. However, the

actions required for a successful CSU are often inadequately planned or executed, resulting in subpar CSU performance. Addressing this significant deficiency is critical to identifying activities necessary to enhance the likelihood of successful CSU performance in capital projects. Drawing upon insights from CSU experts, objective data collection, and subsequent analysis. Additionally, elements such as the timing of critical success factors (CSF) implementation, support for safety and quality, and the current frequency of CSF achievement need to be developed. The study in “Critical Success Factors for Commissioning and Start-Up of Capital Projects” highlights six particular lagging CSFs that demand attention: CSU value recognition, adequate funding for CSU, CSU leadership continuity, establishment of system milestone acceptance criteria and deliverables, incorporation of CSU systems engineering during front-end engineering design, and emphasis on systems-focused detailed design. The findings are valuable for capital project team members, including representatives from both owners and contractors, as well as researchers involved in the planning and execution of CSU for facilities [1].

For a general fermentation process a stirred tank fermenter, complete with necessary accessories and automatic control systems for dissolved oxygen, pH, anti-foam, impeller speed, aeration rate, and temperature are needed. Set-point control and compilation of operational parameters are facilitated by software. The pH-electrode is calibrated using pH 4 and 7 buffers. Following this, the oxygen probe was calibrated to 0% using N₂ compressed air and to 100% using air-saturated compressed gas. [2]

In the architecture, engineering, and construction (AEC) sector, manual compliance checking proves to be labor-intensive, time-consuming, costly, and prone to errors. Over the past 50 years, extensive research has been conducted on automated compliance checking (ACC) to enhance the efficiency and precision of this process. Despite the development of numerous ACC systems, they are limited to handling

requirements with quantitative metrics or specified properties. Consequently, approximately 53% of building requirements still require manual verification, primarily due to inherent ambiguity. The ambiguity surrounding building requirements is poorly understood in existing literature, hindering both accurate interpretation and automated checking [3].

The primary aim of this project is to establish a cutting-edge fermentation laboratory facility designed to the distinct requirements of biotechnology and biopharmaceutical research and production. This overarching objective encompasses a series of pivotal goals, including but not limited to, meticulously designing the facility layout to optimize workflow and efficiency, selecting state-of-the-art equipment calibrated to meet the demands of advanced bioprocessing techniques, refining processes to enhance productivity and yield, integrating stringent safety measures to safeguard personnel and product integrity, executing thorough commissioning procedures to ensure seamless functionality, and conducting rigorous validation protocols to validate the facility's performance and compliance with regulatory standards. By meticulously addressing each of these objectives, the project endeavors to create an innovative and fully functional laboratory environment conducive to pioneering advancements in biotechnological and biopharmaceutical endeavors.

METHODOLOGY

The methodology for achieving the research objectives outlined in the project's problem statement is designed to address each key goal of the project, including facility design, equipment selection, process optimization, safety implementations, commissioning, and validation.

Beginning by revisiting the project's objective and the specific goals outlined in the problem statement. This provides a clear understanding of the research objectives that the methodology aims to achieve. Describe the overall approach that will

guide the research process. This may involve a combination of qualitative and quantitative methods, depending on the nature of the research objectives. For the facility design, it is going to be discussed the criteria considered for designing the fermentation laboratory facility, such as space utilization, layout efficiency, and compliance with regulatory standards. Considering the equipment selection choosing appropriate fermentation equipment, considering factors like scalability, compatibility with processes, and maintenance requirements is important for this part of the process. Outline the safety measures implemented to ensure the well-being of personnel and compliance with safety regulations. Describe protocols for handling hazardous materials and emergency procedures. Finally, describe the procedures for commissioning the facility and validating processes to ensure they meet regulatory standards and produce consistent results.

The methods used for collecting data throughout the project could include observational studies, surveys, interviews, research, or experimental data to ensure, for example, that the best decision of equipment is being made and how this data is being analyzed. A detailed timeline with relevant milestones and activities required to complete each phase of the project. Include estimated due dates or timeframes for completing each activity to provide a clear overview of the research timeline serves as a roadmap for project management and helps track progress towards completion.

By following this methodology and adhering to the research schedule, it aims to achieve the project's objectives efficiently and effectively. The methodology provides a structured framework for conducting research and making informed decisions throughout the project lifecycle.

RESULTS AND DISCUSSION

Fermentation laboratory design is a multidimensional process that encompasses the careful integration of physical infrastructure,

modern equipment, and robust operational protocols tailored to the specific needs of biotechnology and biopharmaceutical research and production. From the layout and spatial organization of the facility to the selection of fermenters, bioreactors, and supplementary equipment, every aspect of the design is meticulously planned to optimize workflow efficiency, ensure process scalability, and maintain stringent safety standards. Factors such as temperature control, agitation, nutrient supplementation, and aseptic conditions are meticulously considered to create an environment conducive to the growth and manipulation of microorganisms for various applications. Moreover, the design incorporates features to facilitate process optimization, regulatory compliance, and future expansion, fostering a dynamic and adaptable research environment. By prioritizing functionality, flexibility, and safety, fermentation laboratory design serves as a cornerstone for advancing scientific discovery and innovation in biotechnology and biopharmaceutical industries.

The fermentation laboratory design project is a crucial part where the findings from the design process are presented and analyzed. The logistics for floor plans and layouts of the fermentation laboratory, highlighting key areas such as fermentation suites, support spaces (e.g., airlocks, cold storage), and utility distribution. The airlock for this laboratory should be separated but connected to the laboratory to ensure personnel gown in before performing any high-level work. The design should optimize space utilization, workflow efficiency, and ergonomics to support research and production activities. The 30L bioreactors should be facing one of the big walls to ensure a direct connection to in-house utilities. As well, Biosafety Cabinets (BSC) should be by a wall to ensure connection to exhaust lines out of the laboratory. The benchtop area for prepping media and other small instrumentations should be placed in the middle of the space to ensure good people flow through the space. Considering the high risk of exposure for some of these processes, the BSC

selection should be the Class II B2 BSC vs the Class II A2. The B2 BSC is more expensive but ensures better protection for the product, environment, and personnel. The air recirculation of this BSC is 100% exhausted to the outside decreasing the risk of exposure as shown in Figure 1 while the A2, 70% of the air is recirculated to the BSC, as shown in Figure 2, making it riskier for high-level organisms. In terms of fermenters, a stainless-steel reactor is necessary to have the capability of being cleaned with chemicals without rusting the tank. Also, this material is resistant to high pressure and steaming cycles for decontamination processes.

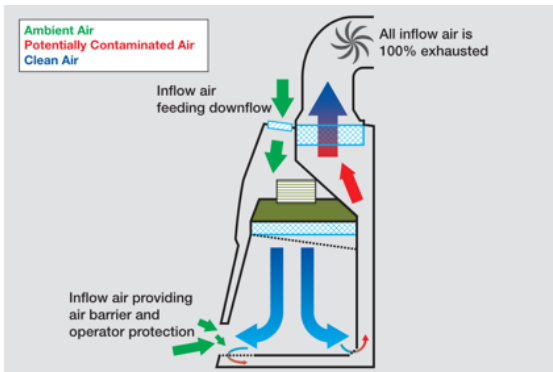


Figure 1
Class II Type B2 BSC [2]

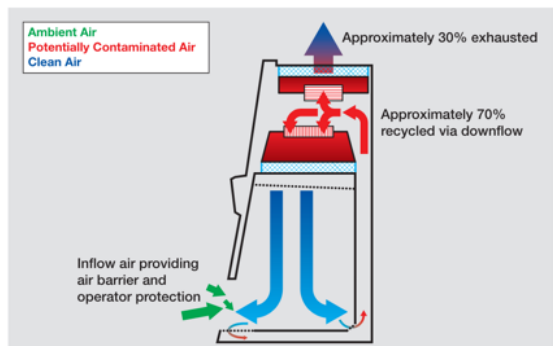


Figure 2
Class II Type A2 BSC [2]

The selection of equipment for a fermentation laboratory holds importance in ensuring the success and efficiency of biotechnological and biopharmaceutical processes. Fermentation equipment serves as the backbone of laboratory operations, facilitating the growth and manipulation of microorganisms for the production of valuable

compounds such as bioproducts. The choice of fermenters, bioreactors, and supplementary equipment directly impacts process scalability, productivity, and product quality. Factors such as vessel size, agitation mechanisms, control systems, and sterility features must be carefully evaluated to align with the specific requirements of the fermentation processes being conducted. Furthermore, the compatibility of equipment with automation systems, data acquisition software, and regulatory standards is crucial for ensuring seamless integration into laboratory workflows and compliance with industry guidelines. By selecting the right equipment, fermentation laboratories can optimize process performance, minimize operational risks, and accelerate scientific discovery and innovation in the field of biotechnology. Figure 3 shows the adequate size fermenter with the appropriate automation (D-DCU) system that better fits the needs of the laboratory for operational scale and screening for process optimization.



Figure 3
30L Stainless Steel Fermenter with D-DCU unit [4]

Process optimization in a well-designed fermentation laboratory is facilitated by the seamless integration of advanced equipment, meticulously planned workflows, and robust experimental protocols. The laboratory's design plays an essential role in providing the necessary infrastructure and resources to conduct systematic

optimization studies effectively. With dedicated fermentation suites equipped with versatile fermenters and bioreactors, researchers can precisely control critical parameters such as temperature, pH, agitation speed, and nutrient supplementation. Additionally, the layout and organization of the laboratory promote efficient workflow management, allowing for seamless transitions between different stages of experimentation and data collection. Advanced monitoring and control systems provide real-time feedback, enabling researchers to fine-tune process parameters and optimize production yields and product quality. Moreover, the availability of support spaces, such as media preparation and analytical laboratories, enhances the efficiency of optimization studies by ensuring timely access to necessary materials and analytical tools. Overall, a well-designed fermentation laboratory serves as a cornerstone for process optimization, empowering researchers to unlock the full potential of biotechnological and biopharmaceutical applications through meticulous experimentation and data-driven decision-making.

Safety implementation in a fermentation laboratory is fundamental to ensuring the well-being of personnel, protecting the environment, and safeguarding the integrity of research and production processes. A comprehensive approach to safety begins with the design of the laboratory itself, incorporating features such as containment systems, ventilation controls, and designated areas for hazardous materials handling (like base cabinets, acid cabinets, and flammables cabinets) to ensure all the chemicals are stored properly. Rigorous training programs educate personnel on proper handling procedures, emergency protocols, and the use of personal protective equipment (PPE). Regular risk assessments identify potential hazards associated with fermentation processes, allowing for the implementation of mitigation strategies and the development of contingency plans. Strict adherence to regulatory standards, such as Good Laboratory Practices (GLP) and biosafety guidelines, further enhances safety protocols.

Continuous monitoring of laboratory operations, coupled with proactive maintenance of equipment and infrastructure, helps mitigate risks and ensure compliance with safety regulations. By prioritizing safety at every stage of operation, fermentation labs uphold a culture of responsibility and accountability, fostering a secure environment conducive to innovative research and production endeavors.

Commissioning and validation are critical stages in the lifecycle of a fermentation laboratory, ensuring that equipment, processes, and facilities meet regulatory requirements and perform as intended. During commissioning, all systems and equipment are thoroughly tested to verify functionality and performance. This includes mechanical checks, system integration tests, and calibration of instrumentation. Once commissioning is complete, validation activities are conducted to demonstrate that fermentation processes consistently produce results within predefined specifications. This involves executing validation protocols, collecting data, and analyzing results to confirm process robustness and reliability. Regulatory compliance, adherence to industry standards, and alignment with quality management systems are paramount throughout commissioning and validation efforts. By rigorously assessing and documenting the performance of the fermentation laboratory, commissioning and validation activities ensure the integrity, safety, and efficacy of research and production processes, enhancing confidence in stakeholders and regulatory authorities.

In a fermentation laboratory, it's essential to acknowledge and address limitations while also considering future directions for improvement and innovation. Limitations may include constraints such as budget restrictions, space limitations, or technological barriers that impact the lab's capabilities and effectiveness. These limitations should be carefully documented and considered when planning future initiatives to ensure realistic expectations and effective resource allocation. Additionally, future considerations may involve exploring opportunities for expanding research

capabilities, adopting emerging technologies, or enhancing process efficiency and sustainability. By proactively identifying and addressing limitations while strategizing for the future, fermentation laboratories can continually evolve to meet the evolving needs of biotechnology and biopharmaceutical research and production, fostering innovation and driving scientific advancement.

CONCLUSIONS

In conclusion, the comprehensive design and operation of a fermentation laboratory are vital for the success of biotechnology and biopharmaceutical research and production endeavors. Throughout the discussion, we have explored various key aspects, including facility design, equipment selection, process optimization, safety implementations, commissioning, validation, and considerations for the future. Each of these components plays a crucial role in ensuring the efficiency, safety, and regulatory compliance of the laboratory. By integrating advanced technologies, rigorous safety protocols, and systematic validation procedures, fermentation laboratories can maximize productivity, uphold quality standards, and facilitate innovative advancements in the field. However, it is essential to recognize and address limitations while continuously seeking opportunities for improvement and adaptation to meet the evolving needs of the industry. Through collaborative efforts and a commitment to excellence, fermentation laboratories can remain at the forefront of scientific innovation, driving progress and breakthroughs in biotechnology and biopharmaceutical research.

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