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RISK ASSESSMENT IN DEVELOPMENT OF TECHNICAL REQUIREMENTS FOR DESIGNING FERMENTATION EQUIPMENT IN ACCORDANCE WITH REQUIREMENTS OF GOOD MANUFACTURING PRACTICE

The object of research is the risks arising at the stage of cultivation of biological agents in fermentation equipment. The starting point of the life cycle of equipment, including fermenters, is the terms of reference, which defines all the necessary requirements that must be taken into account in the design, manufacture, installation and qualification. One of the most important and important stages of the equipment life cycle is the formation of a holistic and complete technical specification, which would allow taking into account all critical process parameters already at the stage of developing the design of the fermenter in accordance with the requirements of good manufacturing practice. It is important to note that the regulatory documents of the pharmaceutical industry (good manufacturing practices, good engineering practices, etc.) do not form specific requirements for equipment and processes, but only define general approaches to ensuring the quality system.

The study used the principles of risk management, which are advisable to use throughout the entire life cycle of the equipment. The analysis of the stages of sanitary preparation (washing, disinfection and rinsing), sterilization of the fermenter and the cultivation process made it possible to determine the risks arising at the corresponding stages of production and ways to solve them. The approach to the analysis of critical parameters proposed in this work can be used to improve the development of technical specifications for a fermenter. Thanks to this, at the initial stages, a comprehensive approach to risk management is provided, which in turn will prevent the negative impact of external factors on the final product. Another aspect of using the research results is the possibility of forming fermenter validation protocols. The results obtained in this work can also be used in the development and scaling of the cultivation process for the production of active pharmaceutical ingredients in biopharmaceutical production.

Keywords: fermenter design, cultivation of biological agents, active ingredient, pharmaceutical substance, good manufacturing practice.

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1. Introduction

The production of active pharmaceutical ingredients (API) using biological agents (BA) at the stage of cultivation is ensured through the use of special equipment – fermenters.

A priori, the BA stage (cultivation) is a critical process in biopharmaceutical production. This is primarily due to the process of biological synthesis of target substances, during which substances are synthesized, which are isolated and purified at the next stages of the technological process. Therefore, fermenters are a key element of biopharmaceutical production, since at the stage of cultivation, the main qualitative and quantitative indicators of the finished product are formed [1].

The processes of biological synthesis of APIs are usually characterized by high specificity and require fermenters specially designed for the needs of a certain type of BA or the needs of the process [2]. Since the most important first step in the design and manufacture of a fermenter is the User Requirement Specification (URS) [3], it is important to analyze the critical parameters at the URS development stage.

Therefore, *the object of the study* is the risks arising at the cultivation stage of biological agents in fermentation equipment. *The aim of research* is to analyze and evaluate the critical parameters of the cultivation stage for the development of URS for fermentation equipment in accordance with the requirements of good manufacturing practices (GMP).

2. Methods of research

GMP requirements do not give recommendations for making specific design decisions, they only contain basic provisions for organizing production to ensure the release of high-quality, efficient and safe products. For a comprehensive solution of problems in the design, manufacture, operation and maintenance of equipment, a technical assignment is being developed. URS document that specifies the specific hardware, performance, performance and documentation requirements required to obtain a product that meets the previously specified parameters. The development of URS is a necessary stage of the quality system assurance process and without which it is impossible to carry out the project at the proper level.

The general requirements for URS are described in the Good Engineering Practice (GEP) guidelines. When preparing the URS, it is advisable to adhere to the principle that this document is prepared from the beginning of the design or reconstruction, that is, at the beginning of the object's life cycle.

When developing a URS to meet the GMP requirements, it is correct to use the principles of risk assessment to determine their impact on quality (intermediate products and finished products). This concept is laid down in ST-N MHU 42-4.2:2011. Medicines. Quality Risk Management (ICH Q9), which is harmonized with the European Medicines Agency regulatory document EMA/INS/GMP/79766/2011 «Quality Risk Management (ICH Q9)» (EMA/INS/GMP/79766/2011 «Risk Management for quality (ICH Q9)»), which is included in Part III of the EU GMP Guidelines [4].

It is by the number of risks and their influence on the quality of the final product that fermentation processes are referred to as critical processes, and fermenters – to critical equipment [1].

One of the basic functions of the terms of reference is risk management, the analysis of which, as a rule, is carried out during the URS development. Quality risk management is a systematic process of assessing, controlling, reporting and reviewing the risks to the quality of a medicinal product during its life cycle. The general scheme of typical risk management is shown in Fig. 1.

There are two basic principles of quality risk management:

- 1) quality risk assessment should be based on scientific evidence and be directly related to quality maintenance;
- 2) level of effort, formalization and documentation of the quality risk management process should correspond to the level of risk [5].

This study proposes a risk analysis during the culture phase for fermenters operated in batch mode.

Fig. 2 shows an example of the process flow diagram of the cultivation stage.

Let's show a list of risks that need to be taken into account when developing a URS for the development of a fermenter project and suggest engineering design as a way to manage risks [6, 7]:

1. Risks of contamination during pre-fermentation procedures (in this case, it is washing, disinfection, rinsing, sterilization of the fermenter, preparation of utilities, etc.).

2. Risk of contamination during cultivation, which leads to a decrease in cultivation productivity, changes in the qualitative composition of the culture liquid (CL), changes

in the quality characteristics of the API (in this case, it is sterilization of the aeration air, violation of the tightness of the fermenter during the process or sampling, etc.).

3. Risks of violation of technological parameters of cultivation (in this case, it is a change in the intensity of mass transfer processes, violation of thermoregulation modes, etc.).

4. Risk of violation of the biosafety level (in this case, it is the entry of BA into the environment).

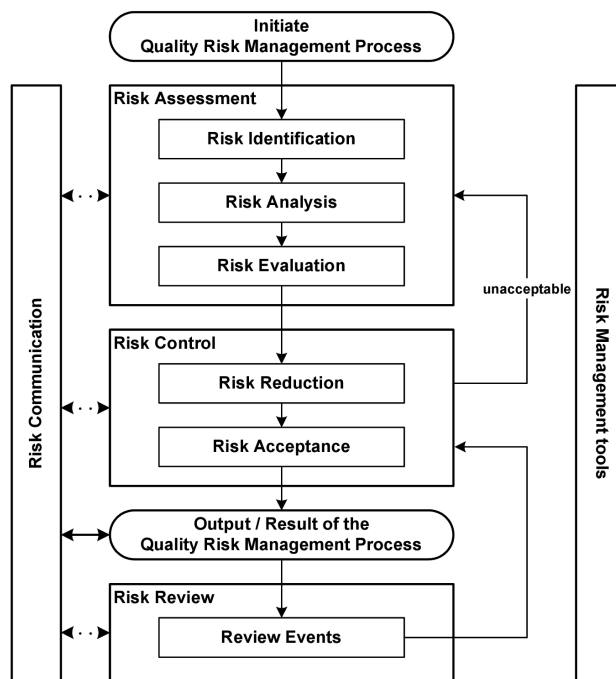


Fig. 1. Risk management scheme [5]

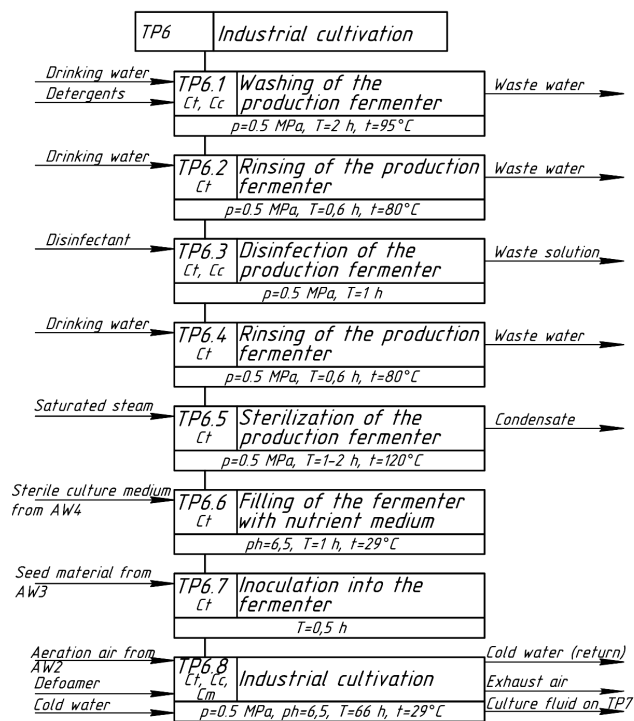


Fig. 2. Technological scheme of the stage of cultivation: AW – auxiliary work, TP – technological process, Tc – technological control, Cc – chemical control, Cm – microbiological control

3. Research results and discussion

3.1. Engineering design of structural fermenter elements as URS part. To formulate requirements for the design or construction of the fermenter, it is possible to use the standard [8], which contains specific requirements for the design features of equipment, valves, piping systems, materials, etc. in biotechnological production.

3.2. Equipment washing. The purpose of the operations is to remove contaminants – substances of various origins – after engineering work, after preliminary cultivation or equipment downtime for more than the specified time. This operation ensures the removal of biological and mechanical contamination factors and allows to reduce the biological load before sterilization procedures.

Risks during washing/disinfection: poor-quality/incomplete removal of contaminants, incomplete removal of residues of cleaning solutions.

A modern technological and constructive solution for risk management when carrying out the listed pre-fermentation procedures is implemented as a CIP operation – Cleaning in Place. For this purpose, in the installation diagram and in the design of the Fermenter, it is necessary to provide for a complete set of fittings for mounting and connecting a mobile or stationary ball head. The type of washing head (rotary, static), their number and location must be selected in accordance with the configuration of the fermenter (diameter and height of the apparatus, the number of nozzles, the configuration of the mixing device). Detergent solution, disinfectant solution and rinse water must circulate in a closed loop.

Compliance with the GMP requirements is implemented by ensuring regulation of the technological parameters of the process – pre-regulated concentration of detergents and disinfectants, frequency of circulation, temperature of the washing solution. The efficiency of washing with water should be controlled by its electrical conductivity and microbiological parameters.

3.3. Sterilization procedures. The purpose of the operation is to achieve a technology-specific level of asepsis.

In pharmaceutical biotechnology, depending on the production capacity of the enterprise and, accordingly, the fermenter capacity, two technological options for sterilization are possible [9]:

1. For large-scale production, it provides for the operation of production fermenters with a volume of more than 25 m³, sterilization of an empty fermenter is carried out, which then receives a sterile nutrient medium.

2. Other technologies are supposed to sterilize the culture medium directly in the fermenter. And this process ensures sterilization of the device itself.

The practice of using enzymatic equipment made it possible to determine that the use of heat treatment with saturated steam is the most correct technological method of sterilization. To manage risks, a complex infrastructure is being created, including automatic cleaning and sterilization systems (Cleaning in Place and Sterilizing in Place – CIP/SIP) and other technical solutions.

Risks in sterilization procedures. In general, the resulting risk in sterilization is non-sterility. The components of this risk are due to uneven distribution of the vapor phase and, accordingly, the temperature field inside the fermenter,

leaks in utilities, uneven heating of utilities (pipelines) and valves. To prevent the occurrence of the listed risks, it is necessary to:

- ensure an even distribution of the vapor phase during air removal (installation of power supply systems – windscreen) and condensate (condensate drains);
- ensure the maintenance of the set temperature inside the fermenter (steam supply to the jacket of the fermenter);
- provide for the use of valves of modern design (membrane or bellows type), which ensure tightness during sterilization;
- ensure the installation of steam locks with condensate drainage;
- provide for the use of modern shaft seals of the mixing device – mechanical seals.

3.4. Cultivation. The purpose of the cultivation stage is to obtain the maximum amount of the target product (metabolite or biomass) within the genetically determined capabilities of BA by providing comfortable conditions in the external environment.

Risks during cultivation, as a rule, associated with a violation of the asepticity of the culture liquid and changes in the technological parameters of cultivation.

Asepsis violation of the culture liquid, as a rule, is caused by the «breakthrough» of biological contaminants through the aeration air sterilization system, violation of the tightness of engineering communications and structural elements of the fermenter. And also, the risks caused by incorrect performance of the sampling procedure and incorrect control of process indicators.

The risks related to the technological parameters of cultivation include changes in the intensity of heat and mass transfer processes, which are caused by the instability of the multiphase dispersion, to which CL belongs.

To prevent biological contamination associated with a violation of the quality of the individual filters, effective manipulations are needed to pre-sterilize them and to prevent sharp fluctuations in air velocity during cultivation with constant control of the air pressure drop before and after the filter.

To manage risks regarding changes in the technological parameters of cultivation, due to mass transfer processes and heat transfer processes, it is required to develop an automatic control system based on the use of adequate mathematical models. An essential element of correct engineering design is to equip the fermenter with modern control sensors and controls. The objects of control and devices are (Fig. 3):

- monitoring and control of the speed of rotation of the shaft of the mixing device;
- dissolved oxygen concentration sensor (pO₂ sensor);
- sensor for the concentration of dissolved carbon dioxide;
- pH sensor;
- CL level sensor;
- pressure sensors;
- temperature sensors (in the fermenter, jacket, air, etc.).

The number of continuous online measurements that can be practically monitored in a fermenter is surprisingly small. As a rule, they are limited by pressure, CL level, temperature, pH (acidity/alkalinity) [10].

For the sensors to work correctly, procedures for their calibration, cleaning, use and storage must be developed.

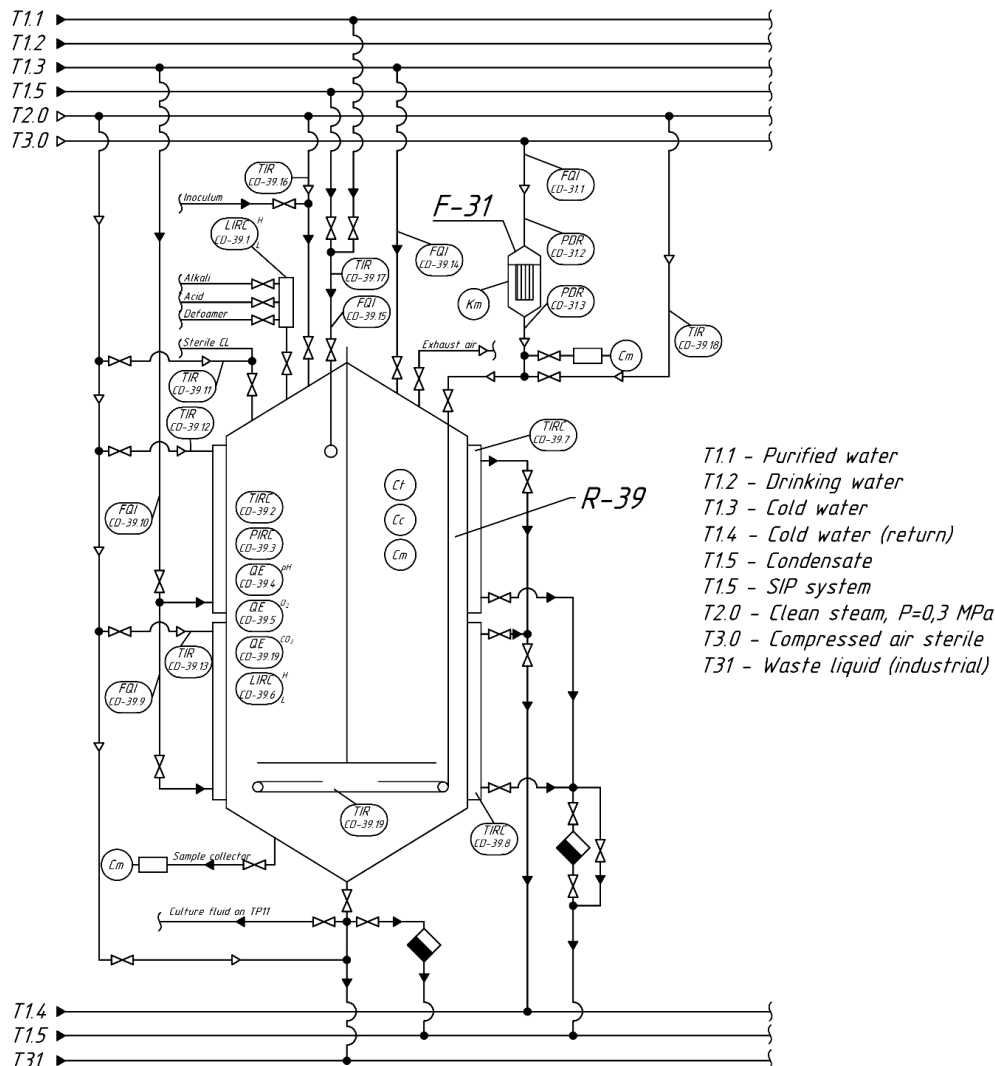


Fig. 3. Hardware circuit of the fermenter with control and measuring devices: F-31 – individual aeration air filter, R-39 – fermenter

The entire automation system must be connected and controlled by the SCADA (Supervisory Control and Data Acquisition) system. SCADA systems are a computer monitoring and control system that centrally collects, displays, and stores information from remote transducers and data acquisition sensors to support the management of equipment, devices, and automated functions. In both cases (research and production), oversight is an important part of SCADA. This functionality allows to perform procedures automatically without operator intervention [11]. The SCADA system must meet the requirements of GMP, 21CFR Part 11 and be validated.

4. Conclusions

It is shown that biotechnological processes for the production of active pharmaceutical ingredients during the cultivation of biological agents are implemented in fermenters, which, in the presence of a significant number of risks, are referred to as critical equipment. To meet the requirements of good manufacturing practice for obtaining products of guaranteed quality, proven effectiveness and established safety, it is advisable to use a risk management scheme, starting from the URS development stage. In the course of the research, an analysis of the critical stages of the cultivation process was carried

out and options for engineering design were proposed. The research results can be used in the formation of the URS, in the design of fermenters, in the formation of specifications for the purchase of fermenters and will allow at the initial stages of the project to implement a risk management system. The results obtained can be used in the development of new designs of fermenters in order to determine the necessary directions for improving their structural elements.

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