AFDC 11 (3021) DTZS
ICS 07.080

DRAFT TANZANIA STANDARD

Biotechnology - Large-scale process and production Part 1: Guidelines for fermentation and downstream processes

TANZANIA BUREAU OF STANDARDS

0 Foreword

This Tanzania Standard supports industrial activities in the area of biotechnology covering operations with both non-genetically and genetically modified micro-cells including microorganisms, either non-pathogenic and pathogenic cells

Fermentation processes vary widely in their nature and design. Generally, prokaryotic or eukaryotic micro-organisms, plant cells, mammalian cells or insect cells are cultivated and processed in such a way as to produce a desired end-product such as biomass, pharmaceuticals, additives, metabolites and foodstuffs

This standard was prepared to ensure product quality, safety of personnel and the environment in biotechnology fermentation and downstream processes.

During the development of the standard, reference was made to the following documents:

- BS EN 12075: 1997 *Biotechnology - Large-scale process and production - Procedures for fermentation and downstream processes*, published by British Standards Institute (BSI).

1 Scope

This Tanzania Standard specifies the guidelines for fermentation and downstream processes in large scale operations.

2 Normative References

The following referenced documents are indispensable in the application of this Tanzania standard. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies:

AFDC 11 (3023) DTZS Biotechnology - Large scale process and production - Guidance for the handling, inactivating and testing of waste

3 Terms and definitions

For the purposes of this Tanzania standard, the following terms and definitions should apply:

3.1 bioaerosol

Colloid dispersed solid or liquid particles in a gaseous environment presenting negligible gravitational settling, containing micro-organisms.

3.2 biocontamination

undesired biological substances such as micro-organism, allergens, toxins

3.3 closed system

System where a barrier separates micro-organisms/organisms from the environment

3.4 controlled area

Area constructed and/or operated in such a manner as to limit contamination of the other areas by micro-organisms/organisms from within the controlled area.

3.5 downstream process

Sequence of operations following the fermentation.

3.6 fermentation

Biotechnical process where the target product is formed while cultivating the process cell(s)

3.7 fermenter

Closed or open vessel where a cell culture is grown under controlled conditions.

3.8 hazard

Intrinsic potential property or ability of something (e.g. any agent, equipment, material or process) to cause harm.

NOTE. Harm is an injury or damage to health of people and/or to the environment.

3.9 inactivation

partial or full destruction of a given activity up to destruction of the microbiological system

3.10 master cell bank (MCB)

Stock of cells from which all subsequent cell banks are derived.

NOTE 1. MCB stock is not normally intended for use directly in production.

NOTE 2. The term MCB covers all type of cells i.e., micro-organisms as defined in 3.11

3.11 micro-organism

Any microscopic biological entity, cellular or non-cellular, capable of independent replication or replication within host cell,

3.12 pathogen

Micro-organism causing disease.

3.13 physical containment

System for confining a micro-organism/organism or other entity within a defined space.

3.14 process micro-organism

Micro-organism used for production purposes in a biotechnological process or constituting (part of) the product itself.

3.15 risk

Probability of occurrence of a hazard causing harm and the degree of severity of the harm.

3.16 sterilization

Validated process used to reach a state free from viable micro- organisms.

NOTE. In a sterilization process, the nature of microbiological death or reduction is described by an exponential function. Therefore, the number of micro-organisms that survive a sterilization process can be expressed in terms of probability. While the probability can be reduced to a very low number, it can never be reduced to zero.

3.17 unit operation

Operation to perform a single chemical, physical or mechanical activity.

NOTE 1. Examples of unit operations are heat transfer, mixing, separating including filtration and centrifugation, and sterilization.

NOTE 2. Combinations of unit operations constitute a process step. For example, downstream process step could consist of separation, extraction, concentration and drying.

3.18 waste

By-product arising from a process or unwanted substance or article derived from any activity.

NOTE. Examples of waste are scrap material, effluent, unwanted residue or surplus arising from any process or activity or any substance or article which is discarded or to be disposed of as being broken, contaminated, spoiled, or worn out

3.19 working cell bank (WCB)

Stocks of cells derived from the master cell bank (MCB), which are used for inoculation.

NOTE. The term working cell bank covers all type of cells i.e. micro-organisms as defined in 3.11.

4 Process description

4.1 General

Fermentation and downstream processes consist of a number of unit operations linked together to produce a product. There is a wide range of unit operations and can be categorized into process steps which are described in 4.2 to 4.5.

4.2 Raw materials

Select, transport, store and treat raw materials so that required characteristics are retained and contamination with unwanted materials or micro-organisms is prevented. Carry out medium preparation according to documented procedures for treatment, addition and mixing of the raw materials.

4.3 Fermentation

4.3.1 Ensure that the fermenter and associated equipment are cleaned and sterilized as appropriate to the process and risk assessment (see clause 5).

4.3.2 Prepare the inoculum culture from the working cell bank. Typically, this process consists of one or more stages of increasing volume, such that the amount transferred to the production stage in most cases is between 2 % and 10 % of the production volume. Checks on culture against specified requirements can be carried out at each stage, especially for aseptic operation.

4.3.3 Carry out transfers or terminations of each inoculum stage as appropriate in accordance with documented procedures for transfer, including contamination criteria.

4.3.4 Run the main fermentation in an appropriate mode such as batch, fed batch, continuous, semi-continuous or multistep process or any combination of these. The process micro-organism can be contained in the fermenter in a variety of modes such as free suspension, immobilized in a matrix or retained on a membrane. Terminate the fermentation and continue the downstream process.

4.4 Downstream process

4.4.1 Use appropriate downstream processes for the isolation and/or further purification, concentration and stabilization of the product. These processes can occur either during or after the fermentation process and, in some cases, can occur in the fermenter itself.

4.4.2 Unit operations used in downstream processes can include filtration, centrifugation, precipitation, distillation, lyophilisation, crystallisation, ion exchange, chromatography, electrodialysis, direct and tangential filtration, liquid-liquid extraction, flotation, evaporation.

4.5 Output

4.5.1 Package, label, store and transport products with due regard to safety and quality according to appropriate documented procedures and/or national regulations/standards.

4.5.2 Establish waste management procedures for the waste products from the process including provisions for contaminated or aborted process material. Waste from biotechnological processes shall be handled and, if necessary, inactivated in accordance with AFDC 11 (3023) CD1.

5 Risk management

5.1 Risk assessment

5.1.1 A documented risk assessment shall be made for the micro-organism and process with regard to the general hazards identified. This will typically be done at the stages of process design, process implementation, significant process change.

5.1.2 A relevant method of risk assessment shall be used with regard to personnel, environment and product.

5.1.3 The risk group of the micro-organism shall be considered in preparing the assessment

NOTE 1. This assessment can be based on methods such as: HACCP (Hazard Analysis Critical Control Points), HAZOP (Hazard and Operability)

NOTE 2. In some cases of traditional or empirically processes, the risk assessment can take a simplified form based on a history of safe use.

5.2 Description of relevant risks

The risk assessment shall take into account the hazards from the potential exposure, such as:

a) release of bioaerosol;

b) biocontamination of raw materials or any part of the process which can result in the production of a pathogen or harmful substance;

c) deliberate or unintentional variation in the composition of raw materials, or any variation of process parameters which could allow physiological variation, leading to the presence of harmful substances or pathogens;

d) direct contact with micro-organisms;

e) failure of containment.

5.3 Control of risks

5.3.1 Process design

Based on the results of the risk assessment, the risks to personnel, products and environment shall be minimized by choosing the appropriate unit operations, procedures and equipment. At the same safety level, this selection will also take into account the type of product and the economics of the process.

5.3.2 Procedural reviews

Procedures to monitor the effectiveness of the designated controls shall be established and reviews held at regular intervals.

5.3.3 Biocontamination

The nature and extent of any biocontamination of the process shall be monitored and the potential risks and hazards arising shall be assessed taking into account the experiences with the process. Levels of acceptable biocontamination shall be determined. Procedures shall be established to inactivate biocontaminated materials, equipment and controlled areas in cases which present unacceptable risks to personnel and/or the environment.

NOTE. Occasional contamination of biotechnological processes occurs, although the frequency of such occurrences can be extremely low. It is recognized that in some traditional industries (for example production of wines) natural introduction of micro-organisms from the environment is a routine or essential feature of the process.

5.3.4 Documentation

To ensure control of raw material and process, and to contribute to product quality, documentation shall be established so that the documented risk control procedures are applied. The operating conditions and methods of monitoring and control shall be defined and results recorded such that control of the process can be demonstrated. In the case of unexpected events, training and procedures shall be established to enable operating staff to regain control of or stop the process in a safe manner.

NOTE. A system of quality management, such as ISO 9000 series should be used.

5.3.5 Preparation, cleaning and sterilization of equipment

The methods of preparation of the equipment shall be defined. Techniques for cleaning and sterilizing, such as the use of chemicals, steam or heat, shall be verified.

5.3.6 Procedural controls based on the risk assessment

Depending on the risk group of the process micro-organism (see 5.1) and on the specific circumstances of the process in which it is present, different parts of the process can require different levels of physical containment as given in Table 1

Table 1. Physical containment levels based on the risk assessment

Requirement[1]	**Physical containment level**			
	1	**2**	**3**	**4**
Areas to production areas restricted to nominated workers only	No[2])	Optional[3])	Yes[4]), recommended via airlock	Yes, via airlock
Viable micro - organisms containment in a closed system	No	Yes	Yes	Yes
Closed system to be located within a controlled area	No	Optional	Yes	Yes
Sample collection, addition of materials to a closed system and transfer of viable micro -organisms to another closed system, performed so as to:	No	Minimize release	Prevent release	Prevent release
Exhaust gases from the closed system treated so as to:	No	Minimize release	Prevent release	Prevent release
Bulk culture fluids not removed from the closed system unless the viable micro-organisms	Optional	Inactivated by validated means	Inactivated by validated chemical or physical means	Inactivated by validated chemical or physical means

[1]) When using this table, attention is drawn to existing national regulations concerning the requirements within a biotechnical area.
[2])No: No special requirements for safety (but could be put in place for other reasons for instance, quality)
[3]) Optional: Should be decided case-by-case basis subject to risk assessment, the extent to which these measures are to be applied.
[4]) Yes: Requirement.