International Standard

ISO 12370

Guidelines for treatment and reuse of fermentation-based pharmaceutical wastewater

Lignes directrices pour le traitement et la réutilisation des eaux usées pharmaceutiques issues de la fermentation

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Contents

Page

iTeh Standards
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Document Preview
ISO 12370:2025
https://standards.iteh.ai/catalog/standards/iso/7cdc33a5-a37a-4825-a9f6-311e21198df7/iso-12370-2025

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This document was prepared by Technical Committee ISO/TC 282, *Water reuse*, Subcommittee SC 4, *Industrial water reuse*.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

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Introduction

With the development of the social economy and the improvement of people's living standards, the public's demand for drugs to improve the quality of life and prolong lifespan is continually increasing. Pharmaceutical manufacturing ranks among the top five industries in the global economy. Fermentation-based pharmaceuticals, such as analgesics, anti-inflammatory drugs, antibiotics, lipid regulators, receptor blockers and X-ray contrast agents, have been widely used in health treatment. At the same time, the impact of drug pollution and pharmaceutical wastewater discharge has become a global hot topic of concern for environmental protection. At present, traces of drugs have been detected in sewage wastewater, drinking water and rivers in many different places, including the United States, China, Australia, Europe and Africa, and research shows that one of the reasons is the discharge of pharmaceutical wastewater.

Pharmaceutical manufacturing is generally divided into two categories: biopharmaceutical production and chemical pharmaceutical production. Fermentation-based pharmaceutical production is one kind of biopharmaceutical production with a long history of development, relatively advanced technology and wide application. Fermentation-based drugs include antibiotics, vitamins, amino acids and other types of drugs. The fermentation pharmaceutical production process not only requires a stable supply of pure water, but also produces a large amount of wastewater. Studies have found that such wastewater usually contains high levels of waste solvent, refractory organic matter, residual drugs and salt. Meanwhile, for different production processes, such as bacteria screening, refining and purification, drying, packaging and other steps, the concentration of pollutants in organic wastewaters varies greatly. The chemical oxygen demand (COD_{Cr}) can reach 4 410 mg/l to 40 000 mg/l.

The rapid development of the fermentation-based pharmaceutical production industry also poses challenges to the treatment and discharge of wastewater, as well as the management of water resources. If wastewater is released into the environment without effective treatment, pharmaceutical pollutants will cause water-quality risks, thus adversely affecting the aquatic ecosystem and public health. In recent years, many countries have put forward new requirements for the reclamation treatment of industrial wastewater and introduced many laws and regulations on the reuse of the treated wastewater, requiring treated wastewater to be reused in various applications, such as in-plant production, greening and irrigation. However, there is still a lack of reasonable technical specifications for the reclamation treatment and reuse of fermentation pharmaceutical industry wastewater in terms of how to select the most suitable treatment technology for each type of wastewater and how to efficiently recycle or reuse the wastewater.

This document is intended to help solve the current technical problems regarding the treatment and reuse of fermentation-based pharmaceutical wastewater. In view of the particularity of the production processes generating fermentation-based pharmaceutical wastewater, this document puts forward the general recommendations of the process flow and technology selection for reuse of wastewater after treatment under different pollution loads. At the same time, according to the different reuse scenarios of treated wastewater, different reuse water treatment technologies are recommended to meet the reuse requirements in each scenario. This document can provide theoretical support and technical guidance for the treatment and reuse of fermentation-based pharmaceutical wastewater. At the same time, it can be conducive to promoting technology advancement, product upgrading, energy conservation and emission reduction of fermentation-based pharmaceutical enterprises. Moreover, it can promote the standardized and the high-quality development of fermentation-based pharmaceutical wastewater treatment and reuse projects, improve water efficiency and thus promote a more sustainable and high-quality development of the whole industry.

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Guidelines for treatment and reuse of fermentation-based pharmaceutical wastewater

1 Scope

This document provides technical guidance for fermentation-based pharmaceutical wastewater treatment and reclamation for different reuse purposes.

This document contains information on pollution loading, general principles and applicable wastewater treatment and reclamation treatment. In addition, example processes for wastewater treatment and reclamation are listed to support different treatment conditions and reuse purposes.

2 Normative references

The following documents, in whole or in part, are normatively referenced in this document and are indispensable for its application. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 20670:2023, *Water reuse — Vocabulary*

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3 Terms, definitions and abbreviated terms

For the purposes of this document, the terms and definitions given in ISO 20670:2023 and the following apply.

ISO and IEC maintain terminology databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at https://www.electropedia.org/

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3.1 Terms and definitions

3.1.1
denitrification
reduction of nitrate and nitrite to the end product nitrogen (in the form of gas) by the action of bacteria

[SOURCE: ISO 11733:2004, 3.6]

3.1.2
fermentation-based pharmaceutical wastewater
process and non-process wastewater generated in the production operations of fermentation pharmaceutical enterprises

Note 1 to entry: Process wastewater refers to the in-situ residual mother liquor and wastewater produced in the process of *fermentation-based pharmaceutical production* (3.1.3). Non-process wastewater refers to wastewater produced by cooling or cleaning equipment and from washing ground surfaces.

3.1.3
fermentation-based pharmaceutical production
process of producing antibiotics or other active pharmaceutical ingredients by fermentation and producing drugs through separation, purification, refining and other processes

Note 1 to entry: The types of drugs can be divided into antibiotics, vitamins, amino acids and other categories.

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3.1.4
hydraulic retention time
theoretical average period of time that influent wastewater remains in the biological reactor

Note 1 to entry: The hydraulic retention time (HRT) is calculated as net biological reactor volume (m^3) divided by the daily influent wastewater flow (m^3/d).

3.1.5
kettle liquid
liquid left at the bottom after distillation in a distillation column

3.1.6
basic on-site domestic wastewater
water that contains only human body waste and human liquid waste, and can contain grey water from washing, but does not contain commercial or industrial discharges

[SOURCE: ISO 24513:2019, 3.2.2.2.1]

3.2 Abbreviated terms

B/C ratio	ratio of BOD_5/COD_{Cr}
BOD_5	five-day biochemical oxygen demand
COD_{Cr}	chemical oxygen demand by dichromate method
IFAS	integrated fixed-film activated sludge
MBR	membrane bioreactor
MLSS	mixed liquor suspended solids
MLVSS	mixed liquor volatile suspended solids
NH_3-N	ammonia-nitrogen
NO_3-N	nitrate-nitrogen
NTU	nephelometric turbidity unit
SS	suspended solids
TN	total nitrogen
TP	total phosphorus
UASB	upflow anaerobic sludge blanket

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4 Pollution loading

4.1 Classification of wastewater

The typical process configuration for fermentation-based pharmaceutical production and the main wastewater generation links are shown in Figure 1.

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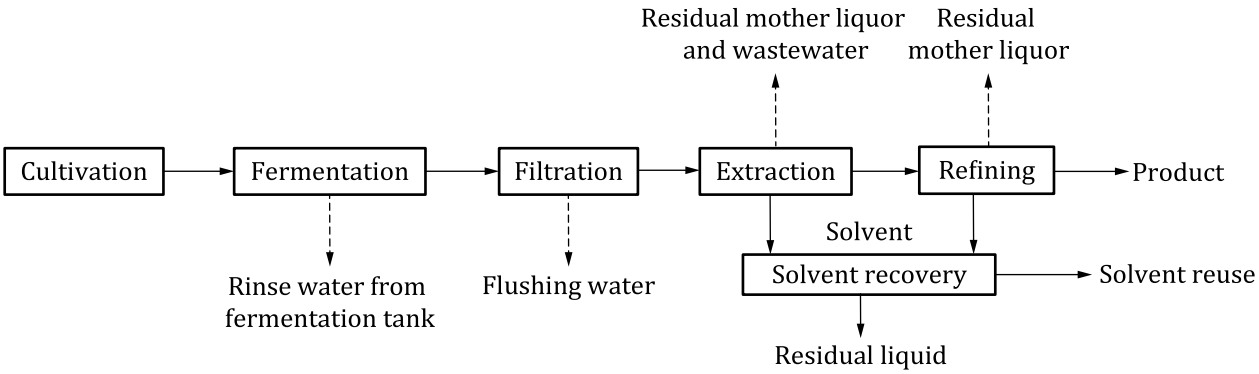

Figure 1 — Typical processes and wastewater generation links for fermentation-based pharmaceutical production

Fermentation-based pharmaceutical wastewater is classified as follows:

a) Process wastewater: residual mother liquor and wastewater generated in the process of fermentation-based pharmaceutical production, such as extraction residual mother liquor, refining residual mother liquor or resin regeneration wastewater.

b) Non-process wastewater: production flushing drainage (e.g. equipment flushing water, ground flushing water), dynamic system drainage (e.g. drainage from recirculating cooling water system and once-through cooling water), etc.

4.2 Wastewater volume

Measured data should be used for quantifying the amount of wastewater generated in the fermentation-based pharmaceutical production process. The total amount of wastewater discharge should be measured and determined at the point of final discharge from the factory, and the process wastewater discharged from each production process should be measured individually.

When there is no actual measurement data available, analogous survey data can be used. The amount of wastewater can be determined by analogy with the emission data of existing fermentation pharmaceutical enterprises with the same production scale, similar raw materials and products and similar production processes. Annex A provides further information about pharmaceutical wastewater quality. See Table A.1 for representative generation of wastewater from fermentation-based pharmaceutical production.

If there is no measured or analogous data, this can be estimated using Formulae (1) and (2):

$$Q_y = \Sigma Q_i \tag{1}$$

$$Q_i = \alpha \cdot \beta \cdot Q + T_i \tag{2}$$

where

Q_y is the total wastewater production (m^3/d);

Q_i is the wastewater generation rate of each production process (m^3/d);

α is the reduction factor for generated wastewater calculated according to the water supply, which is determined according to factors such as the production process of the enterprise and the level of water supply and drainage facilities, generally taking 70 % to 90 %;

β is the percentage of sub-item water supply for process water that can be determined according to actual material accounting;

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Q is the production water consumption (m^3/d), which can be determined according to production water quota;

T_i is the amount of water transferred in or out (m^3/d) for this process; the transfer-in is positive and the transfer-out is negative.

4.3 Quality of produced wastewater

The main pollutants in fermentation-based pharmaceutical wastewater are fermentation residues, intermediate products, various organic solvents and inorganic salts residual in the extraction and refining process. Wastewater usually is characterized by complex composition, many kinds of organic pollutants, high COD_{Cr} and BOD_5 values, high NH_3-N concentration, high toxicity and high concentration of SS.

The determination of wastewater quality should be based on the actual monitoring data, and the wastewater generated by each production process should be sampled and analysed individually.

When the wastewater quality does not meet the detection conditions, it can be determined by analogy with the emission data of existing fermentation pharmaceutical enterprises with the same production scale, similar raw materials and products and similar production processes.

In the absence of measured and analogous data, refer to Table A.2 and Table A.3 for typical wastewater quality generated during production.

5 General principles

Before the process design, the water quality and quantity should be comprehensively investigated, and necessary monitoring and analysis should be carried out. In addition, the process design should be based on the water quality characteristics of wastewater and the destination after treatment; the appropriate process flow should be selected after considering reliability and economy.

Wastewater containing hydrocarbons should be equipped with level monitoring equipment for leak detection. Wastewater containing antibiotic active ingredients with biological toxicity or ecological risks should be pretreated separately to eliminate potential biological toxicity and ecological risks before flow into the wastewater plant for overall wastewater treatment and reuse. Furthermore, the environmental risk prevention system should be improved and relevant environmental risk prevention facilities such as accident pools should be set up to ensure that the wastewater can be fully collected and effectively treated under the accident condition and all effluent should meet discharge standards. In addition, measures such as oxidation and disinfection should be adopted to prevent secondary pollution before discharge.

Wastewater generated in each process of fermentation-based pharmaceutical production should be pretreated by quality classification, mixed and discharged as comprehensive and concentrated wastewater for anaerobic biological treatment to improve the biodegradability of wastewater, and then mixed with low-concentration wastewater for aerobic biological treatment. Basic on-site domestic wastewater contains numerous biodegradable organics, which can meet the basic demands of the microorganisms in activated sludge. It also provides sufficient carbon sources and nutrients for microbial growth. At this stage, the pretreated basic on-site domestic wastewater can also be added according to the quality of wastewater to increase the B/C ratio. Reclamation treatment of secondary treated effluent can be conducted to further remove contaminants. The overall treatment flow chart of fermentation-based pharmaceutical wastewater is shown in Figure 2.

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