Gemensamma författningssamlingen avseende hälso- och sjukvård, socialtjänst, läkemedel, folkhälsa m.m.

ISSN 2002-1054, Artikelnummer 88518007HSLF
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HSLF-FS 2018:7
Utkom från trycket den 23 mars 2018

Läkemedelsverkets föreskrifter om ikraftträdande av reviderad monografi för fermentationsprodukter i Europafarmakopén och om supplement 9.4 till Europafarmakopén;

beslutade den 15 mars 2018.

Läkemedelsverket föreskriver följande på förslag av Svenska farmakopékommittén och med stöd av 9 kap. 11 § läkemedelsförordningen (2015:458).

1 § Monografin för fermentationsprodukter i nionde utgåvan av Europafarmakopén (European Pharmacopoeia Ed. 9.0) ska ersättas med monografin enligt bilaga 1 till dessa föreskrifter.

2 § Supplement 9.4 till den nionde utgåvan av Europafarmakopén (European Pharmacopoeia Ed. 9.0) ska gälla som föreskrifter i Sverige och komplettera den nionde utgåvan av Europafarmakopén och dess supplement 9.1, 9.2 och 9.3 samt den reviderade monografin för fermentationsprodukter i frågor som rör läkemedelslagen (2015:315).

3 § De svenska namn på monografierna som anges i bilaga 2 ska användas i all den produktinformation för berörda läkemedel som krävs enligt gällande regler. De ändringar av svenska namn som anges i bilaga 2 ska vara genomförda i sådan produktinformation senast den 1 april 2023.

Dessa föreskrifter träder i kraft den 1 april 2018.

Läkemedelsverket

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NOTE ON THE MONOGRAPH

Due to the public health risk associated with histamine contamination (see for example: Public Health Risks of Histamine and other Biogenic Amines from Fish and Fishery Products, Meeting report, 23-27 July 2012 FAO headquarters, Rome Italy), further requirements related to the quality of raw materials were added to the Raw materials section of the monograph.

The present monograph was adopted by the European Pharmacopoeia Commission by correspondence on 12 January 2018. The date on which the states party to the Convention on the Elaboration of a European Pharmacopoeia shall implement, within their territories, the revised version of the monograph has been set to 1 April 2018.

04/2018:1468

PRODUCTS OF FERMENTATION

Producta ab fermentatione

This monograph applies to indirect gene products obtained by fermentation. It is not applicable to:

- *monographs in the Pharmacopoeia concerning vaccines for human or veterinary use*;
- *products derived from continuous cell lines of human or animal origin*;
- *direct gene products that result from the transcription and translation from nucleic acid to protein, whether or not subject to post-translational modification*;
- *products obtained by semi-synthesis from a product of fermentation and those obtained by biocatalytic transformation*;
- *whole broth concentrates or raw fermentation products.*

This monograph provides general requirements for the development and manufacture of products of fermentation. These requirements are not necessarily comprehensive in a given case and requirements complementary or additional to those prescribed in this monograph may be imposed in an individual monograph or by the competent authority.

DEFINITION

For the purposes of this monograph, products of fermentation are active or inactive pharmaceutical substances produced by controlled fermentation as indirect gene products. They are primary or secondary metabolites of micro-organisms such as bacteria, yeasts, fungi and micro-algae, whether or not modified by traditional procedures or recombinant DNA (rDNA) technology. Such metabolites include vitamins, amino acids, antibiotics, alkaloids and polysaccharides.

They may be obtained by batch or continuous fermentation processes followed by procedures such as extraction, concentration, purification and isolation.

PRODUCTION

Production is based on a process that has been validated and shown to be suitable. The extent of validation depends on the critical nature of the respective process step.

CHARACTERISATION OF THE PRODUCER MICRO-ORGANISM

The history of the micro-organism used for production is documented. The micro-organism is adequately characterised. This may include determination of the phenotype of the micro-organism, macroscopic and microscopic methods and biochemical tests and, if appropriate, determination of the genotype of the micro-organism and molecular genetic tests.

PROCESSES USING A SEED-LOT SYSTEM

The *master cell bank* is a homogeneous suspension or lyophilisate of the original cells distributed into individual containers for storage. The viability and productivity of the cells under the selected storage conditions and their suitability for initiating a satisfactory production process after storage must be demonstrated.

Propagation of the master cell bank may take place through a seed-lot system that uses a working cell bank.

The *working cell bank* is a homogeneous suspension or lyophilisate of the cell material derived from the master cell bank, distributed in equal volumes into individual containers for storage (for example, in liquid nitrogen).

Production may take place by batch or continuous culture and may be terminated under defined conditions.

All containers in a cell bank are stored under identical conditions. Once removed from storage, the individual ampoules, vials or culture straws are not returned to the cell bank.

PROCESSES USING STAGED GROWTH IN CULTURES

The contents of a container of the working cell bank are used, if necessary after resuspension, to prepare an inoculum in a suitable medium. After a suitable period of growth, the cultures are used to initiate the fermentation process, if necessary following preculture in a prefermentor. The conditions to be used at each stage of the process are defined and must be met with each production run.

CHANGE CONTROL

If the production process is altered in a way that causes a significant change in the impurity profile of the product, the critical steps associated with this change in impurity profile are revalidated.

If a significant change has taken place in the micro-organism used for production that causes a significant change in the impurity profile of the product, the critical steps of the production process associated with this change, particularly the procedure for purification and isolation, are revalidated.

Revalidation includes demonstration that new impurities present in the product as a result of the change are adequately controlled by the test procedures. If necessary, additional or alternative tests must be introduced with appropriate limits. If the change in the process or in the micro-organism results in an increase in the level of an impurity already present, the acceptability of such an increase is addressed.

When a master cell bank is replaced, the critical steps of the production process must be revalidated to the extent necessary to demonstrate that no adverse change has occurred in the quality and safety of the product. Particular attention must be given to possible changes in the impurity profile of the product if a modified or new micro-organism is introduced into the process.

RAW MATERIALS

The raw materials employed in the fermentation and/or down-stream processing are of suitable quality for the intended purpose. They are tested to ensure that they comply with written specifications. Special attention must be paid to the levels of free histidine in fish peptones as the presence of free histidine may lead to histamine formation in certain conditions.

Levels of bioburden in media or in the inlet air for aeration are reduced to an adequately low level to ensure that if microbial contamination occurs, it does not adversely affect the quality, purity and safety of the product. Addition of components such as nutrients, precursors, and substrates during fermentation takes place aseptically.

IN-PROCESS CONTROLS

In-process controls are in place to ensure the consistency of the conditions during fermentation and down-stream processing and of the quality of the isolated product. Particular attention must be paid to ensure that any microbial contamination that adversely affects the quality, purity and safety of the product is detected by the controls applied.

Production conditions may be monitored, as appropriate, by suitable procedures for example to control and check:

- temperature,
- pH,
- rate of aeration,
- rate of agitation,
- pressure,

and to monitor the concentration of the required product.

DOWN-STREAM PROCESSING

At the end of fermentation, the producer micro-organism is inactivated or removed. Further processing is designed to reduce residues originating from the culture medium to an acceptable level and to ensure that the desired product is recovered with consistent quality.

Various purification processes may be used, for example, charcoal treatment, ultrafiltration and solvent extraction. It must be demonstrated that the process or processes chosen reduce to a minimum or remove:

- residues from the producer micro-organism, culture media, substrates and precursors,
- unwanted transformation products of substrates and precursors.

If necessary, suitable tests are performed either as in-process controls or on the isolated product of fermentation.

IDENTIFICATION, TESTS AND ASSAY

The requirements with which the product must comply throughout its period of validity, as well as specific test methods, are stated in the individual monographs.

Namn på monografier i supplement 9.4 till Europafarmkopén

Nya monografier

Engelskt namn	Svenskt namn
Bupleurum root	Harört, rot
Green tea	Grönt te, blad
Guarana	Guarana, frö
Houttuynia herb	Ödleblad, ört
Mate leaf	Mate, blad
Moutan bark	Buskpion, bark
Platycodon root	Praktklocka, rot
Szechwan lovage rhizome	Sichuanloka, jordstam
Formic acid	Myrsyra
Gammadex	Gammadex
Raltegravir potassium	Raltegravirkalium
Soya phospholipids for injection	Sojafosfolipider för injektion
Sucrose, liquid	Sackaros, flytande
Tigecycline	Tigecyklin
Choline ([^{11}C]methyl) injection	Kolin([^{11}C]metyl)injektionsvätska

Ändrade engelska namn

Nytt engelskt namn	Tidigare engelskt namn	Svenskt namn
Metoclopramide hydrochloride monohydrate	Metoclopramide hydrochloride	Metoklopramid-hydrokloridmono-hydrat

Ändrade svenska namn

Svenskt namn	Tidigare svenskt namn	Engelskt namn
Järn(III)kloridhexa-hydrat	Ferrikloridhexahydrat	Ferric chloride hexa-hydrate
Järn(II)fumarat	Ferrofumarat	Ferrous fumarate
Järn(II)sulfat, torkat	Ferrosulfat, torkat	Ferrous sulphate, dried
Järn(II)glukonat	Ferroglukonat	Ferrous gluconate
Järn(II)sulfathepta-hydrat	Ferrosulfatheptahydrat	Ferrous sulphate heptahydrate
Koagulationsfaktor IX (rDNA), human, koncentrerad lösning	Koagulationsfaktor IX human, rekombinant, koncentrerad lösning	Human coagulation factor IX rDNA concentrated solution

Koagulationsfaktor IX (rDNA), human, pulver till injektionsvätska	Koagulationsfaktor IX human, rekombinant, pulver till injektionsvätska	Human coagulation factor IX (rDNA) powder for solution for injection
Koagulationsfaktor VIIa (rDNA), human, koncentrerad lösning	Koagulationsfaktor VIIa, human rekombinant, koncentrerad lösning	Human coagulation factor VIIa rDNA concentrated solution

HSLF-FS kan laddas ner via Läkemedelsverket.
Webb: www.lakemedelsverket.se

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MILJÖMÄRKT
3041 0242
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Elanders Sverige AB, 2018