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5.31. PHAGE THERAPY MEDICINAL PRODUCTS

This general chapter is published for information.

It offers a framework of requirements for phage therapy active substances and medicinal products for human and veterinary use and their production and control.

The provisions of the chapter do not exclude the use of alternative production and control methods that are acceptable to the competent authority.

1. DEFINITION

Bacteriophages (phages) are viruses that infect bacteria and depend on their bacterial host for replication. Phages consist of a genome comprised of single or double stranded DNA or RNA, encapsulated in a protein capsid.

Phage therapy medicinal products (PTMPs) are preparations of naturally occurring or genetically modified phages used to treat or prevent human or veterinary bacterial infections.

A PTMP can contain one phage, i.e. a single phage therapy active substance, or a mixture of phages, combined with excipients. PTMPs can be administered by various routes and are available in different dosage forms.

2. PRODUCTION

2-1. *GENERAL PROVISIONS*

Phages are obtained by propagation in bacterial host strains and are purified using suitable methods.

The production process yields a PTMP of consistent quality and stability. Appropriate in-process testing is implemented at relevant time points and/or key intermediate stages of the process.

Production of PTMPs is based on a well-characterised bacterial cell bank and phage seed-lot system using a host-phage combination that has been shown suitable. Typically, a two-tiered system is used. Where justified, a single-tiered system may be used.

PTMPs may be prepared on-site as doses for an individual or for a few patients, based on specific clinical needs.

PTMPs require an appropriate framework to ensure the desired quality, hereinafter referred to as the quality system. The extent of the quality system is driven by the risks for the patient concerned, such as microbial contamination. Risk assessment is employed to determine the level of risk and the required level of quality assurance to achieve appropriate product quality.

2-2. *BACTERIAL CELL BANKS*

Bacterial host cells used for PTMP production must be described in detail. This includes information on the source of the bacterial strain, subsequent manipulations and the tests used to characterise the strain. This must include determination of its antibiotic susceptibility profile and of the nucleotide sequences of its chromosome(s) and plasmids. The use of bacterial strains whose genome contains sequences coding for detrimental factors (e.g. prophages, antibiotic resistance determinants, toxins) is avoided, unless otherwise justified and authorised.

Bacterial host cells used for PTMP production are derived from a well characterised bacterial master cell bank (MCB) that is of clonal origin and complies with the following requirements:

Identification. The identity is confirmed using a suitable method.

Microbial purity. The absence of microbial contaminants is determined by plating or any other suitable method.

Viability. The number of viable cells is determined by a plate count or any other suitable viable cell count method.

Phage sensitivity. The susceptibility of the strain to the phage therapy active substance is demonstrated using a plaque assay or any other suitable method.

Absence of detrimental phages. The absence of phage particles that could be detrimental to the quality of PTMPs is confirmed.

If a working cell bank (WCB) is used for production, it is a clonal derivative of the MCB and complies with the requirements for MCB.

2-3. *PHAGE SEED LOTS*

Phage seed lots used in PTMP production are derived from a single phage clone and must be characterised in detail. Information on the phage source, nucleotide sequence and susceptible bacterial species and/or strains is to be provided. Other parameters such as plaque morphology or phage morphology are determined, if relevant.

Phages whose genome contains sequences coding for known or potential detrimental genetic factors, e.g. antibiotic resistance determinants, toxins or lysogeny modules, are avoided, unless otherwise justified and authorised. For genetically or chemically modified phages, the modifications must be described and their effects characterised.

A phage master seed lot complies with the following requirements:

Identification. The phage seed lot is identified by a suitable method.

Microbial purity. The absence of microbial contaminants is demonstrated by a suitable method.

Phage purity. The absence of extrinsic phage contaminants is confirmed by a suitable method; however, as intrinsic phages may be unavoidable when using clinical isolates for production, their presence may in this case be justified and authorised when controlled by a suitable method.

Potency. The infectious phage titre is determined by a plaque assay or any other suitable method.

If a phage working seed lot is used for production, it is a clonal derivative of the phage master seed lot and it complies with the requirements for the phage master seed lot.

2-4. *PRODUCTION AND PURIFICATION*

Production of PTMPs is based on a bacterial cell bank and phage seed-lot system, in which cross-contamination between different phages and bacterial host strains is strictly avoided. The genetic stability of the phage is determined by sequencing a suitable number of purified harvests followed by a comparison against the phage master seed lot sequence.

Raw materials of pharmaceutical grade are used. Raw materials of biological origin also comply with the requirements of general chapter *5.2.12. Raw materials of biological origin for the production of cell-based and gene therapy medicinal products*.

Several single harvests of the same phage clone may be pooled before the purification process.

Phages are purified by suitable techniques.

Only a purified harvest containing a single phage therapy active substance that complies with the following requirements may be used in the preparation of the final lot:

Identification. The identity of the phage is confirmed using a suitable method.

Potency. The infectious phage titre is determined by a plaque assay (expressed in PFU/mL or PFU/mg) or any other suitable method.

Microbiological examination (*2.6.12*). The purified harvest complies with the established specification.

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Residual reagents. Based on risk analysis, tests for residues of reagents used during production and posing safety concerns are carried out on the purified harvest.

Host-cell impurities and contaminants. Contaminants and other potentially toxic substances derived from the host cells (e.g. endo- and exotoxins, host-cell proteins, host-cell DNA, temperate phages) are absent or within the established specifications.

2-5. *FINAL LOT*

The final lot can be administered by various routes and may be available in different dosage forms. Additional tests are required, depending on the dosage form and on the route of administration.

When it is not practical, for unlicensed pharmaceutical preparations, to carry out the tests (e.g. batch size, time restraints), other suitable methods are implemented to ensure that the appropriate quality is achieved in accordance with the risk assessment carried out and any local guidance or legal requirements.

A final lot complies with the following requirements:

Appearance. It complies with the established specification.

Identification. The identity of each phage is verified using a suitable method.

Potency. The infectious phage titre of each phage is determined by a plaque assay (expressed in PFU/mL or PFU/mg) or other suitable method and complies with the established specification for the particular preparation.

Microbiological quality. Sterile PTMPs comply with the test for sterility (*2.6.1*). For non-sterile PTMPs, the microbiological quality is determined using a suitable method and complies with the established specification for the particular preparation.

Pyrogenicity. If applicable, the final lot complies with a suitable test for pyrogenicity and with the limit approved for the particular product.

Water content (*2.5.12* or *2.5.32*). Solid PTMPs comply with the limit approved for the particular product.

pH (*2.2.3*). Liquid PTMPs comply with the limit approved for the particular product.

2-6. *ADAPTED PRODUCT*

Phage adaptation (training) is the process by which phages can be directed to evolve in order to increase their potency against (a) clinical isolate(s).

When the adapted PTMP is used in the individual patient that was the source of the clinical isolate, phage adaptation starts with a phage or mixture of phages, each complying with the provisions of section 2-3. The final lot complies with the provisions of section 2-5, unless otherwise justified and authorised. The increased potency of the final lot of the adapted PTMP against the target clinical isolate is confirmed, serving also as an appropriate substitute for the identification test.

3. LABELLING

The labelling requirements outlined in relevant supranational and national regulations apply.

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