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Lääkealan turvallisuus- ja kehittämiskeskus | Säkerhets- och utvecklingscentret för läkemedelsområdet | Finnish Medicines Agency

Solu- ja geeniterapiatuotteiden valmistuksessa käytettävien raaka-aineiden laadusta

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Taustaa

- ATMP tuotteiden valmistuksessa käytettäville raaka-aineille asetettavien laatuvaatimusten harmonisointia tarvitaan. Harmonisointia toivoivat eri sidosryhmät (raaka-aineiden käyttäjät, valmistajat, myyntilupaviranomaiset)
- Euroopan Farmakopeia Komissio päätti kesällä 2012 perustaa raaka-aineiden laatuvaatimuksia pohtivan ryhmän, RCG WP *(Raw Materials for the Production of Cellular and Gene Transfer Products WP)*
- RCG WP koostuu 17 asiantuntijasta, jotka edustavat jäsenmaita, EDQM:ää, EMA:a sekä Australiaa.
- Aluksi RCG WP järjesti sidosryhmätapaamisen kuullakseen eri osapuolia
- RCG WP luonnosteli tekstin 5.2.12., joka julkaistiin yleistä konsultaatiota varten syyskuussa 2014. Sidosryhmien kommentointiaika loppui 2014 lopussa.

Tekstin tarkoitus

- Kyseessä on yleisteksti (general chapter)
- Kattaa solu- ja geeniterapiatuotteiden valmistuksessa käytettävien raaka-aineiden yleiset laatuvaatimukset
- Ohjeellinen, muuttuu pakolliseksi kun monografiassa viitataan kappaleeseen
- Harmonisoi alalla olevia erilaisia käytäntöjä, samalla parantaa vaatimusten ennustettavuutta
- Avustaa tunnistamaan eri raaka-aineiden kriittiset ominaisuudet
- Avustaa hallitsemaan raaka-aineiden valmistuksessa tapahtuvia muutoksia ja eräkohtaisia eroja (batch to batch variation)
- Tarkoituksena **EI** ole lisätä regulaatiota

Tekstin kattavuus (Scope)

Teksti kattaa:

- Biologiset ja biologisesti aktiiviset raaka-aineet: '*Raw materials in this context are defined as biologically active substances used for manufacturing or extracting the active substance(s) but from which the active substance is not directly derived*'
- Esimerkiksi seerumit, kasvutekijät, sytokiinit, proteiinit (rekombinantti ja uutetut proteiinit), vektorit yksin tai yhdessä
- Raaka-aineet jaoteltu eri luokkiin

Teksti ei kata:

- Kompleksiset raaka-aineet, kuten 'feeder cells'
- Soluvapaat matriisit (Acellular matrices, such as decellularised bone)
- Muovit, puskurit
- Sertifiointisysteemi (CEP)
- Tuotantoympäristöön liittyvät GMP asiat

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5.2.12. RAW MATERIALS FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS

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5.2.12. RAW MATERIALS FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY M[illegible]CTS

Vastuu raaka-aineen soveltuvuudesta kuuluu ATMP valmistajalle

This general chapter is publishe[illegible] the quality requirements of raw materia[illegible]d and gene therapy medicinal products for human [illegible]e chapter do not exclude the use of different production and control methods. It is ultimately the responsibility of the user of a raw material to ensure it is of suitable quality for the intended use.

The quality of the raw materials may be considered according to the stage of development of the cell-based or gene therapy medicinal product, thereby acknowledging the inherent evolution of th[illegible]uct during its pharmaceutical and clinical de[illegible] appropriate understanding of, [illegible] when used for the production of ce[illegible]. It should be noted however, that changes in raw mate[illegible]g the lifecycle of the cell-based/gene therapy medicinal product may affect the quality of the medicinal product and thus require additional studies to demonstrate comparability.

Raaka-aineen
laatu ja valmisteen kehitysvaihe:
Raaka-aineen valintaan kannattaa panostaa heti alussa!

…cont

The impact of the raw material on the quality, safety and efficacy of the cell-based/gene therapy medicinal product is evaluated [illegible] approach.
Raw materials are used in order to consis[illegible]
medicinal product of a specified quality in te[illegible]

i) biological activity;
ii) purity/impurity profile;
iii) the risk of adventitious agents (microbiological, viral, etc.).

Riskiarvio jokaisesta raaka-aineesta

From a risk perspective, raw materials free of human or animal substances are preferred.

The biological nature of a raw material used for the production of cell-based/gene therapy medicinal products places special requirement[illegible]quality. Examples of the critical quality attributes specific to e[illegible]ven in this chapter.

Uutta on laatuvaatimusten ’ulottaminen’ raaka-aineiden valmistajiin

It is the responsibility of both the manufacturer and user of a raw material to qualify the raw material in accordance with the above considerations.

1. Scope

This chapter applies to raw materials of biological origin used for the production of cell-based/gene therapy medicinal products. They are used in the manufacture of active substances but the active substance itself is not directly derived from them. The raw materials can be obtained either through extraction or produced by recombinant DNA technology.

This general chapter applies to the following classes of raw materials:

– sera and serum replacements;

– proteins produced by recombinant DNA technology such as growth factors, cytokines, hormones, enzymes and monoclonal antibodies;

– proteins extracted from biological material such [illegible] polyclonal antibodies;

– vectors.

Laatuvaatimukset yksilöity luokittain

The principles of this general chapter may also be [illegible] classes of biological raw materials where appropriate. Chemically synthesised raw materials such as basal media, synthetic peptides or polynucleotides, medical devices and plastics are not within the scope of this general chapter.

2. Risk assessment

Evaluation of the impact of the raw material on the quality, safety and efficacy of cell-based/gene therapy medicinal products must be performed by the user of the raw material. No single measure or combination of measures can guarantee the quality, functionality and safety of a raw material for its intended use. Therefore, a risk assessment must consider the biological origin of the raw material, the production steps applied to it and the ability of the drug product manufacturing process to control or remove the raw material from the final medicinal product.

When evaluating the risk posed by the raw material to the final medicinal product, the potential exposure of a patient to residual raw material is an important risk factor. Any risk factor must be evaluated in relation to the clinical benefit/risk of the cell-based or gene ther

Riskiarviossa tulee
huomioida alkuperä, tuotanto ja
lopputuotteen valmistusprosessin kyky
poistaa raaka-aine
tuotteesta

3. General requirements

3.1. Origin

The origin of the raw material or any substances used for the production of the raw material must be known. Special attention must be paid to aspects related to the sourcing (including pooling) of the substances used in the raw material. Depending on the source of the raw material and its production, raw materials can be divided into:

1) raw materials of human or animal origin;
2) raw materials produced using substances of human or animal origin;
3) raw materials free from substances of human or animal origin.

1) Alkuperä tunnettava
2) Luokitus kolmeen ryhmään alkuperän mukaan
3) Jäljitettävyys!

Due to the inherent risk of transmitting adventitious agents or inducing adverse immune reactions, it is recommended to minimise, wherever possible, the use of raw materials of human or animal origin. If such raw materials are required for the production of cell-based/gene therapy medicinal products, appropriate measures are taken to minimise the risks of transmitting adventitious agents such as viruses, prions, bacteria and protozoa. Traceability of all raw materials is required, especially for those materials with an inherent safety concern.

…cont

For human blood and tissue-derived materials, only carefully selected, healthy donors who are free from infectious transmissible agents may be used. These materials comply with appropriate EU and national legislation. Traceability enables each donation to be unambiguously followed from the donor to the raw material and vice-versa.

When raw materials of animal orig… specific health requirements and ori… consumption. If the origin of the animals … information on their geographic origin is considered.

Jos eläinperäisen
raaka-aineen alkuperää ei täysin tunneta,
vähintään alkuperämaa tunnettava mm.
TSE riskin arvioimiseksi

For substances of human or animal origin, the requirements of chapter *5.1.7. Viral safety* and chapter *5.2.8. Minimising the risk of transmitting animal spongiform encephalopathy agents … apply*

3.2 Production

All raw materials are produced within a recognised quality management system and using qualified production facilities. Suitable in-process controls are developed to ensure that the production process is under control and consistently produces raw materials of defined quality.

…

The production process is optimise
adventitious agents and toxic or harmful
raw material. This can be achieved using one
measures, with justification for the chosen strategy:

– using validated inactivation procedures where possible;

– demonstrating the ability of a production process to minimise, remove or inactivate adventitious agents;

– testing for adventitious agents (virus, bacteria, mycoplasma).

A raw material is produced under aseptic conditions and is sterile, unless otherwise justified. If the raw material is not sterile, the microbiological bioburden must be known.

1) Prosessin kontrollointi – batch to batch
2) Tartuntavaarallisten komponenttien minimointi ja kontrolli
3)Steriiliys

3.3 General quality requirements

Raw materials must meet pre-defined quality requirements for **identity, purity** and **biological activity**. In order to ensure the function of the raw material, it is subject to testing using appropriately qualified methods.

The identity test must reflect the uniqueness of the raw material and distinguish it from other related or similar substances. Impurities include both process-related substances (e.g. in the case of recombinant proteins: host-cell-derived proteins, host-cell-derived DNA and vector-derive[illegible]bstances (e.g. aggregates and degradation pr[illegible]y be expressed either in absolute nu[illegible]for determination of biological activity may

1) Tunnistus (Identity)
2) Puhtaus
3) Pitoisuus
4) Biologinen aktiivisuus

3-3-1. IDENTIFICATION

3-3-2. TESTS (listed)

3-3-3. ASSAY

3-3-4. REFERENCE MATERIAL OR REFERENCE BATCH

4. SERA AND SERUM REPLACEMENTS

4-1. *DEFINITION*

Sera from human or bovine sources and serum replacements (including platelet lysates and other undefined growth additives, conditioned media, blood and other cellular components) are used as growth additives for cell culture. Sera and serum replacements used to promote cellular growth are typically complex biological mixtures, whose exact composition is not always possible to define.

4-2. PRODUCTION

Due to potential differences in quality between batches of serum, cell or tissue lysate, suitable measures are implemented to verify the consistency of each batch before using them as raw materials for the production of cell-based/gene therapy medicinal products. For conditioned media, the removal of the conditioning cells from the media must be validated and potential impurities originating from these cells must be determined for each batch.

4-3. IDENTIFICATION

It is recognised that the exact qualitative composition of sera and serum replacements may be difficult to determine. However, the approximate protein composition in both cases may be determined by, for example, protein electrophoresis. Where relevant, tests for total protein content or any chemical additives are performed. For human serum, the electrophoretic pattern corresponds to that of an appropriate serum reference batch.

4-5. ASSAY

The serum or serum replacement must show growth properties that are within the limits defined for the particular raw material. More than one type of assay may be necessary to show suitability for the intended use.

5. PROTEINS PRODUCED BY RECOMBINANT DNA TECHNOLOGY

5-1. DEFINITION

Proteins and peptides produced by recombinant DNA technology, which are used as raw materials, include growth factors, cytokines, hormones, enzymes and monoclonal antibodies.

Growth factors, cytokines and hormones are substances typically used for stimulation or inactivation, growth promotion or differentiation of cells in cell culture systems.

Other proteins. Enzymes (e.g. collagenases), as raw materials, may be used for extraction of active substances from tissues and/or fluids. Other proteins (e.g. fibronectin) may be used as culture supports or media components.

Monoclonal antibodies used as raw materials include immunoglobulins and fragments of an immunoglobulin with defined specificity. Antibodies can either be conjugated (chemically modified) or non-conjugated. Typical chemical modifications include fluorescent labelling and conjugation to magnetic beads. Antibodies, as raw materials, may be used for selection, activation/stimulation, isolation or purification of cells in cell culture.

5-4. *TESTS (Impurities typical for rDNA products)*

Host-cell-derived proteins and residual host-cell DNA. Where relevant for the particular raw material, the content of residual host-cell DNA and/or protein is determined using a suitable method unless the production process has been qualified to demonstrate suitable clearance. The content is within the limits defined for the particular raw material.

Related proteins. Product-related substances (e.g. antibodies with undefined specificities, glycoforms, degradation and oxidation products, oligomers and aggregates) are determined using liquid chromatography, electrophoretic or immunological methods and are within the limits defined for the particular raw material.

5-5. *ASSAY*

Content. The protein content is determined by an appropriate qualified method, for example by liquid chromatography (*2.2.29*) or UV spectrophotometry.

Biological activity. The biological activity of a recombinant protein can be measured using, for example, cell proliferation, cell differentiation or an enzyme assay. Several acceptable bioassays may exist for a particular protein. For antibodies, cell-based immunoassays and assays based on ligand-binding and affinity may be used

6. PROTEINS EXTRACTED FROM BIOLOGICAL MATERIAL

6-1. *DEFINITION*

Proteins extracted from biological material and used as raw materials include enzymes (e.g. porcine derived trypsin and endonucleases), polyclonal antibodies, other proteins of biological origin (e.g. albumin and transferrin) and peptides of biological origin. They may be of human, animal, plant or microbiological origin.

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6-2. *PRODUCTION*

Proteins are extracted from the blood or tissue of animals or humans, or from plant or microbiological sources using mechanical and/or chemical techniques. They are then subjected to further purification processes using a variety of techniques such as centrifugation, filtration, chromatography and concentration.

…

During production of these proteins, process-related impurities, such as blood components, tissue fragments or contaminating proteins, must be removed. Particular attention is given to product-related impurities.

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… cont

6-4. TESTS

Process-related impurities. Substances derived from the starting material (e.g. blood components, tissue fragments or contaminating proteins) are determined using suitable methods and are within the limits defined for the particular raw material.

Related proteins. Product-related substances (e.g. antibodies with undefined specificity, degradation and oxidation products, oligomers and aggregates) are determined using suitable methods and are within the limits defined for the particular raw material.

6-5. *ASSAY*

Content. The protein content is determined using an appropriate qualified method, e.g. liquid chromatography (*2.2.29*) or UV spectrophotometry.

Biological activity. Where relevant, the biological activity of a protein can be measured using, for example, enzyme assays, immunoassays or assays based on cell proliferation/differentiation. For trypsin, the assay may be performed as described in the monograph *Trypsin (0694)*. Where relevant, the biological activity is expressed per milligram of total protein (specific activity).

7. VECTORS

7-1. *DEFINITION*

Vectors that may be used as raw materials in the production of cell based and gene therapy medicinal products include DNA vectors (e.g. plasmids produced by recombinant DNA technology) as well as viral and bacterial vectors. In most cases they are unique and description of their origin, structure and safety is required.

7-2. *PRODUCTION*

For viral vectors, the production is based on a well-characterised cell bank system and a virus seed-lot system, while for bacterial vectors and plasmids, it is based on a cell bank system. The cell banks must be qualified with respect to identity, viability, strain, genotype/phenotype and presence/copy number of the vector, where relevant. The virus seed lots must be qualified for identity, concentration and infectious titre.

The structural elements, such as the vector or plasmid backbone, regulatory sequences, type of insert and selection markers (including antibiotic resistance sequences) are described.

When using viral or bacterial vectors, consideration must be given to pathogenicity and virulence in man and deletion of virulent determinants where appropriate. The use of replication-deficient viral vectors is preferred from a risk point of view.

5.2.12. RAW MATERIALS FOR THE PRODUCTION OF CELL-BASED AND GENE THERAPY MEDICINAL PRODUCTS

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http://pharmeuropa.edqm.eu

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