Guideline on Quality, Non-clinical and Clinical Assessment of Extracellular Vesicles Therapy Products (Guidance for Industry)

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MINISTRY OF FOOD AND DRUG SAFETY
National Institute
of Food and Drug Safety Evalution

Cell and Gene Therapy Products Division
Biopharmaceuticals and Herbal Medicine
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This guidance provides considerations on the development of extracellular vesicles therapy products in more plain language and represents the current stance of the MFDS on this topic.

This document should be viewed as only recommendations since it is not intended to be legally binding and does not impose any obligations upon industry despite the word 'should' used herein. Besides, since this guidance is written based on the established scientific and technological experiences, and valid laws as of December, 2023, its interpretation and application may vary if necessitated by revision of relevant laws and/or new scientific discoveries, etc.

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1. Scope

The purpose of this guideline is to provide considerations for the development of therapy products using extracellular vesicles (EVs) that are secreted by cells or transgenic cells into which foreign genetic material is introduced. This guideline outlines principles that underpin the quality, nonclinical, and clinical considerations to support the development of EV therapy products with the assurance of consistency in quality, safety, and efficacy.

EVs are lipid bilayer-delimited particles released by cells, and EV therapy products are defined as pharmaceutical products manufactured using EVs produced by living cells through a series of steps for their isolation and purification. Therefore, the definition of EVs in this guideline is not applicable to unisolated and/or non-purified cell suspensions or cell lysates. In addition, EV mimetics created by physical disruption of cells are also excluded from the scope of this guideline. However, if there is a development program intended to use EV mimetics, this guideline may apply and certain characteristics of the product may warrant additional considerations.

This guideline applies to EV therapy products manufactured using EVs released by cells that are derived from humans, animals, or microorganisms. On the other hand, for EV therapy products based on EVs from cells of other origins (e.g., plant cells), additional considerations may be necessary other than those provided in this guideline, considering the characteristics of each cell type.

2. Applicable Regulations

Although EV therapy products are expected to exert pharmacological activity similar to that achieved by cell therapy products, they are not classified as cell therapy products because EV therapy products do not contain living cells.

However, EV therapy products are manufactured from raw materials or substances originating from living organisms and classified as drug products that require special controls for the protection of public health. Therefore, they are regulated as a type of biological products specified by the Minister of Food and Drug Safety.

Given that EV therapy products are based on microvesicles formed directly from cell membranes, they should undergo quality, safety, and efficacy assessments similar to those required for cell therapy products; if EVs of interest are manufactured through genetic modification, they may be classified as gene therapy products.

For EV therapy products based on cells into which foreign genetic material is transferred, they may be subject to the criteria for the assessment of gene therapy products as prescribed in the Act on the Safety of and Support for Advanced Regenerative Medicine and advanced Biological Products as well as this guideline.

For the assessment of EV therapy products, not only the Pharmaceutical Affairs Act and its sub-regulations but also other relevant statues, such as the Bioethics and Safety Act, the Act on Cord Blood Management and Research, and the Blood Management Act, and their respective sub-regulations may apply.

3. Quality Considerations for EV Therapy Products

For the production of EV therapy products, comprehensive considerations should be given to the following:

Characterization of starting materials for producing EVs;
Manufacturing methods for, isolation and purification, and characterization of EVs;
Quality controls;
Stability.

3.1 Characterization of Starting Materials for EV Production

The important points to consider in the characterization of EVs are the origin of the tissues or cells that secrete EVs and cell donor type (e.g., autologous, allogeneic or xenogeneic). Procedures for collecting cells used to produce EVs, eligibility criteria for donors/recipients, and their health status and medical history should be documented. Prior to collecting tissues from a donor, screening for symptoms of infection is absolutely necessary. For donor eligibility criteria for cell or tissue production of EVs, Guideline on Eligibility Determination for Donors of Cell Therapy Products applies.

For the production of EVs, differences in the EVs that may ensue from donor-to-donor variability should be considered since donor diversity may lead to the production of EVs that display different functional characteristics. To ensure the quality of EV therapy products, it is important to isolate appropriate production cells or generate and control an appropriate working cell line, and it is also important to maintain various characteristics that may affect the quality of the product during production culture within adequate ranges. For the manufacture of EV therapy products, autologous human cells, allogeneic human cells such as mesenchymal stem cells, induced pluripotent stem cells (iPSCs)/embryonic stem cells (ESCs), and their cell lines are used. For these cells to be used in manufacturing, their suitability should be evaluated in advance except

for autologous human cells, as described in Guideline for Cell Bank Evaluation of Cell Therapy Products.

If EVs are derived from immortalized clonal cell lines, stringent testing of genotypic and phenotypic stabilities of the cells should be conducted during their production. Stringent testing is required because data are lacking on the phenotypic stability of this type of cell that has undergone a prolonged period of serial passage during the establishment of the cell line. Besides, when EVs are produced using cells that originating from iPSCs/ESCs or immortalized clonal cell lines, consideration should be given to the potential for tumor formation when cell-derived DNA, or EVs derived from tumorigenic cellular impurities mixed into the cell line are adventitiously introduced into the product.

3.2 Manufacturing Methods, Isolation/Purification, and Characterization

Manufacturing EV therapy products involves living cells, meaning even minor changes in cell culture can significantly affect the manufacturing processes and biological properties of EVs, ultimately leading to alterations of the physiochemical and biological characteristics of the cells.

As EVs are isolated primarily from supernatant liquid, followed by purification steps, cell culture conditions should be standardized and batch-to-batch reproducibility should be demonstrated. There are factors that may have a significant impact on the yield and quality of EVs, which include but are not limited to inoculation during cell passaging in manufacturing and cell density/confluence at harvest, viability and appearance of cells, passaging methods, passage number, doubling time, concentrations of oxygen and carbon dioxide, culture temperature, media additives, media composition, culture vessels. In addition, it has been reported that cells cultured in serum-free media or bovine EV-depleted media exhibit differences in their intrinsic characteristics, compared with those cultured in media that contain fetal bovine serum (FBS); furthermore, the yield or quality of the EVs secreted by the cells may be affected.

For the manufacture of EVs, it is crucial to control the viability of

EV-producing cells as apoptotic bodies produced by cells undergoing apoptotic cell disassembly or other cellular components may be present as impurities.

In addition to the origin of EVs, the sources of all the reagents used in the production of EVs should be described. Use of animal-derived substances such as FBS should be avoided whenever possible. Animal-derived reagents may lead to transmission of infectious agents and/or increase undesirable immunological responses in the recipient. If FBS is used as a growth supplement for cell culture media, bovine serum-derived EVs may be introduced into the product, leading to unwanted biological effects. Therefore, if the use of FBS is planned for the production of EVs, it is recommended that only strictly-controlled FBS should be permissible for use, such as FBS that is shown to be free from viruses of bovine origin. Use of reagents free of animal-derived substances or recombinant proteins is encouraged, if posssible.

For isolation and purification of EVs, methods such as ultrafiltration, ultracentrifugation, precipitation, or chromatography may be employed, or two or more of these techniques may be paired for use. According to some experimental reports, EV isolation methods may influence the integrity and functional properties of EVs, such as their morphological and quantitative aspects including protein and nucleic acid profiles, as well as biodistribution in animal studies. Therefore, isolation methods should be standardized with regard to the reproducibility, purity, impurities, and functional properties of EVs, and a detailed description of the isolation methods used should be provided to demonstrate the reproducibility of the methods. Special attention should be paid to the potential presence of residual components other than target EVs even after the completion of the isolation process. It is necessary to establish manufacturing methods with pre-defined markers for process-derived impurities and product-related impurities for use in key steps of the purification process, and consider setting the comparison of pre- and post-purification levels of impurities as an established condition for manufacturing and control. In addition, careful consideration should be given to the stability of EVs

(degradation and generation of variants) during manufacturing or storage.

As EVs are greatly affected by the conditions of cells and manufacturing processes, profiles of the composition and content of proteins, RNAs, and lipids of EVs should be characterized to show that the EVs isolated and purified by specific manufacturing processes display consistency in their characteristics. The content of proteins, RNAs, and lipids should be analyzed by measuring the respective ratios of proteins, RNAs, and lipids to the total number of EVs, together with quantification of the total amount of each constituent. For the content profiling of EVs, advanced methodologies (e.g., LC-MS/MS) should be used to ensure the quantification of the maximum numbers of biomolecules such as proteins, RNAs, and lipids. In addition, developers need to compare proteins identified in their isolated EVs against those identified in other EVs using EV databases. Although there are known general EV markers such as tetraspanins (CD9, CD63, and CD81) and factors regulating late endosome formation (Tsg101 and Alix), none has been characterized as EV-specific markers yet; and therefore, it is important to apply multiplexed profiling of EVs for an array of EV-derived markers that are fit for purpose. Also, in addition to EV-specific protein molecules, semi-quantitative analysis of at least 3 types of proteins, including components not associated with EVs, is recommended.

For EVs, the structure of lipid bilayers, size distribution, and EV proportion in the total cell-derived particles should be investigated using high-resolution image analysis methods (e.g., cryoelectron microscopy (Cryo EM)) and single particle tracking techniques (e.g., nanoparticle tracking analysis (NTA)). When high-resolution image analysis is used, information captured in both close-up and wide-field images should be assessed.

It is recommended that the biological activity of EVs be analyzed in a multi-faceted fashion with multiple potency assays established based on the pharmacological action of the EVs that was identified by assessing their mechanism of action. The following may also be considered for

assessment; quantification of the active components of EVs (e.g., miRNAs, mRNAs, proteins) or measurement of their activities, assessment of cell proliferation and migration, toxicity, activation and suppression of immune cells, regulation of gene expression, and signalling. We recommend that the activity values of EVs be measured using a standard unit based on particle numbers or protein content. In addition, functional activities of EVs attributable to dose escalation should be measured quantitatively. In this case, it is important to establish controls that can exhibit minimum anticipated functional effects. For example, MOCK-EVs obtained from culture medium (maintained at 37° C as those used for manufacturing) to which no cells were added may be used as a control. Such controls provide information on the "background effects" in inducing functional activities of EVs as well as the respective percentages of the contributions made by water-soluble factors and EV-bound factors to the functional activities of the EVs.

Characterization data that include the composition, physiochemical properties, and biological activity of EVs are also essential to demonstrate comparability after a change in the manufacturing process such as manufacturing methods and isolation methods.

Characterization of impurities is also required. For residues from materials used (e.g., serum albumin, antibiotics), data on the methods employed for the removal of the residues and their concentrations should be submitted. Other than EVs containing active substances, as EVs void of such substances or EV variants denatured or degraded during the manufacturing/storage process may exist in EV preparations, it is necessary to establish appropriate manufacturing processes with a capability to remove non-target EVs or their variants to the fullest extent possible. Besides, viruses, microorganisms, mycoplasma, ingredients of culture media, and reagents could possibly be mixed into EV preparations during the process of cell culture, purification/enrichment, and formulation. Consequently, it is necessary to establish qualitative and quantitative assays and assess the acceptance criteria for impurities. Our recommendations for impurity assessment are as follows: either measure

the ratio of intended EVs by means of EV particle profiling as an indicator for the assessment of substances adventitiously introduced into EV preparations, or conduct comparative assessment by titration of EVs using a biological assay and a standard unit based on particle counts.

3.3 Quality Controls of EV Therapy Products

3.3.1 Appearance

For "appearance" testing, a set of criteria should be set to ensure that the outward characteristics and presentation of the drug product are sufficiently identified. Appearance testing aims to determine whether the fundamental outward appearance of the product is acceptable by gross examination. For injectable products, immediate containers into which the drug is filled (e.g., vial, syringe, and bag) should be inspected macroscopically. For products to be thawed prior to use, the pre-thaw and post-thaw color, presentation, and so forth of the drug substance and drug product should be covered as well in the test.

3.3.2 EV Counts

For EV therapy products, quantifying the number of EVs is the most direct way to identify the dose of active components within a drug product, similar to content testing for other pharmaceutical products. The number of EVs that are filled into the container should be representative of the drug substances/ingredients and their quantities of the product.

EVs can be enumerated, along with the measurement of their size distribution, using single particle analysis techniques, such as nanoparticle tracking analysis (NTA), resistive pulse sensing (RPS), and flow cytometry. However, the existing NTA method based on detecting the light scattered from particles cannot differentiate co-isolated non-EV particles of similar size from actual EVs; therefore, NTA data should be compared with other test results (e.g., protein content).

It is important to collect samples in a way that maximizes homogeneity across the samples, and also increase the accuracy of test results by repeat testing each time lot release testing is conducted.

3.3.3 Size of EVs

The size distribution of EVs can be measured using techniques such as NTA, dynamic light scattering (DLS), RPS, and flow cytometry. When single particle analysis is used, it is desirable to depict the size of EVs using a diameter distribution, not just limited to statistical values (e.g., mean, mode, and median).

3.3.4 Mycoplasma

Although EV therapy products are not supposed to contain any cells in the final products, contamination might occur due to the use of raw materials/reagents of animal origin during cell-derived EV production, and EV isolation and purification steps, or by contaminants present in the facilities/environment. Mycoplasma present within EVs should be controlled as it may have impact on the safety of study subjects.

It will be appropriate to collect samples for mycoplasma testing at optimal time points when mycoplasma can be most easily obtained. In general, it is desirable to use culture media and cells pooled at the end of the final cell culture, which is a step immediately prior to EV isolation and purification. If a rapid detection method (e.g., nucleic acid amplification test (NAAT)) is used, its comparability to a compendial culture-based method should be determined.

3.3.5 Adventitious Virus

As EV therapy products are manufactured using cells, there exist a potential for viral contamination and such viruses are directly related to patient safety, and therefore, it is highly critical to demonstrate the absence of viral contamination in the products.

For adventitious virus testing, it is desirable to use culture media and cells collected at the end of the final cell culture, which is an immediately prior step to EV isolation and purification. As virus removal is very challenging to achieve during the process of EV purification, and as the enrichment process is highly likely to increase virus concentration, virus testing of the post-enrichment product should be considered.

3.3.6 Sterility

Sterility testing aims to determine whether finished products are contaminated with microorganisms (bacteria or fungi) and, in principle, should be conducted in compliance with analytical methods described in the official compendia recognized by Minister of Food and Drug Safety, such as the Korean Pharmacopoeia. Besides, the compatibility of the measuring methods and culture media should be tested.

Although finished EV therapy products are not supposed to contain any cells, contamination might occur due to the use of raw materials/reagents of animal origin during cell-derived EV production, and EV isolation and purification steps, or by contaminants present in the facilities/environment, which may result in compromising the quality of the EVs. For this reason, the conduct of sterility testing is recommended as part of the in-process control testing, accompanied by environmental monitoring.

3.3.7 Endotoxin

As endotoxin contamination may arise from operators at the site or from various types of culture media/reagents (e.g., serum, cell growth factor, differentiation inducer) used during the manufacturing process of EV therapy products, it is necessary to confirm the absence of contamination at the stages of drug substance and drug product.

Test specifications should be established considering drug substances and/or the mode and duration of administration of the drug product, body weight, etc., and one of the compendial assays listed in the Korea Pharmacopoeia, which are gel-clot, turbidimetric, and chromogenic methods, should be selected and used.

Depending on the assay selected, a validation study should be conducted first to ensure that the method can detect endotoxins with the level of precision and effectiveness as described in the Korea Pharmacopoeia, and then endotoxin testing should be conducted for each batch using the selected analytical technique with a defined dilution factor.

3.3.8 Identity

Identity testing aims to confirm the ingredients contained in the drug substance or drug product to be the intended active ingredient, that is, EVs, and allows for the identification of their basic properties including the types or activities of the EVs, by means of various markers and test methods. It is recommended that identity testing should include morphological, immunological, and biological analyses that have the capabilities to identify the essential properties of the EVs, where different markers are selected for each of the properties to be investigated.

To date, as there are no known EV-specific markers, enriched EV proteins, RNAs or lipids should be measured to define EV identity. Several proteins, RNAs or lipids should be selected based on the characterization data on EV composition, and test results on the selected components, at the very least, the outcomes obtained using a semi-quantitative method, should be provided.

These components include those expected to be present in or on EVs to be isolated, such as membrane proteins, cytoplasmic proteins that can bind to EV membranes, lipid bilayer components, and miRNAs.

3.3.9 Purity

① Intracellular proteins not associated with EVs

For purity control, criteria should be established on several different types of proteins that are not expected to be enriched in EVs, such as nuclear proteins (e.g., nucleus, mitochondria, golgi body, endoplasmic reticulum).

② Process-related impurities

Appropriate criteria should be established to control residues from the materials used for manufacturing (e.g., serum, albumin, antibiotic).

3.3.10 Potency

Previous studies have shown that proteins or RNAs (e.g., miRNAs) carried by EVs have their own contributory roles associated with biological functions of EV therapy products including mechanisms of action.

Given the complexity of the molecular cargos of EVs, however, EVs are expected to exert their functions in a complex way. As therapeutic effects conferred by EVs cannot be elucidated solely by profiling of EV components performed for characterization, bioanalytical methods should be established to predict the functional characteristics of the EVs.

Following the validation of the analytical methods for their suitability for the intended use, the methods are allowed to be used in potency testing and should be reflective of the expected mechanism of action of the EVs. For example, when the EVs are intended to mediate immunosuppression in vivo, T-cell proliferation assay may be selected as a potency test for the ex vivo assessment of the immunomodulatory characteristics of the EVs. When potency testing is conducted ex vivo using EVs, dose-dependent activities of the EVs should be investigated. The appropriateness of the criteria for potency assays should be evaluated in nonclinical and clinical studies.

For in vitro functional analysis, dose-response relationships should be assessed quantitatively. If an in vivo potency assay is used to verify certain therapeutic effects elicited by EVs, the relevance of the selected animal species for the assay should be described.

3.4 Stability of EV Therapy Products

For the quality assessment of EV therapy products under defined storage conditions (temperature, duration), stability testing should be conducted in accordance with Regulation on Stability Test of Pharmaceuticals (MFDS Notification).

4. Nonclinical Considerations for EV Therapy Products

As a general rule, nonclinical assessment of EV therapy products should be conducted in compliance with the basic principles applied to nonclinical assessment of biological products. It is necessary to evaluate the effects exerted by EV therapy products on efficacy, safety pharmacology, distribution, general toxicity, genotoxicity, immunogenicity or tumorigenicity/oncogenicity, etc.

4.1 Data on Pharmacological Actions

4.1.1 Efficacy

For the efficacy assessment of EV therapy products, dose-escalation studies should be conducted in animal species relevant to the purpose of the studies, and toxicity evaluation may occur in parallel.

Sponsors are encouraged to conduct comparative studies using appropriate controls to demonstrate activities specifically induced by EV therapy products. Culture media, EVs isolated from unstimulated cells, or EV-depleted samples may be considered for a negative control.

4.1.2. Safety Pharmacology

When adequately enriched EVs are administrated and disintegrated, components from inside and outside the EVs may be distributed widely across all organs, which may result in the development of undesirable pharmacodynamic characteristics associated with patient safety. For this reason, EV therapy products generally require the conduct of safety pharmacology studies. Safety pharmacology endpoints may be incorporated into toxicology studies, if possible.

4.1.3 Absorption, Distribution, Metabolism, and Excretion (ADME)

Biodistribution of EVs may affect off-target toxicity of the product, as well as its therapeutic efficacy. Therefore, it is essential to gain a thorough understanding of the EVs' pharmacokinetic properties in designing a clinical study, such as in vivo absorption, distribution, persistence, and clearance including blood concentration and tissue distribution of the EVs.

Most biodistribution studies of EVs may be conducted utilizing detection methods to track the EVs by means of a staining dye or genetically engineered proteins (e.g., expression of GFP or luciferase), or by labeling the EVs with radioisotopes or nanoparticles.

Lipophilic fluorescent dyes, commonly used for in vivo tracking of EVs, such as PKH67, DiD, and DiR, are inserted into the lipid bilayer of the EV membrane. The biggest concern in using these staining dyes is that they display prolonged half-lives ranging from 5 days up to over 100 days. This may lead to the persistence of a staining dye even after the degradation of the dye-labeled EVs, which would generate inaccurate spatiotemporal information on the EVs.

Moreover, as these membrane stains disappear following aldehyde-mediated fixation or lipid extraction, limitations are posed to in vivo analysis of EVs using immnunostaining (immunocytochemistry/i mmunohistochemistry).

When staining-based methods are used, there is a possibility that only staining reagent, bereft of the dye-labeled EVs, is administered, and the injected staining reagent may bind to serum proteins, circulating cells, or blood vessels, complicating the interpretation of the results. To avoid this consequence, testing should be performed to demonstrate the removal of unbound staining reagent by techniques such as sucrose gradient centrifugation or size-exclusion chromatography. The reliability of EV labeling techniques can be verified using electron microscopy or by identifying the correlation between fluorescence expression and EV markers.

To obtain an accurate EV biodistribution profile in consideration of the aforesaid disadvantages of labeling approaches, it will be appropriate to conduct biodistribution studies employing two different test methods, for example, using fluorescent staining in parallel with PCR or immunostaining that is used to identify RNAs or proteins. Furthermore, the additional use of radioisotope-based tools may be considered since

data on the radiochemical yield, purity, and stability may be conducive to interpreting test results.

To ensure the validity of the results from biodistribution studies, additional data may be required to confirm that the labels or genetic modifications used for the analysis have no impact on the biological activity of the EVs. For the methods used, validation data should be provided, showing that the methods have an appropriate level of sensitivity, including the limit of detection (LoD), limit of quantification (LoQ), accuracy, and precision, as well as reproducibility indicating that reproducible results are produced. Additionally, tests to calculate the half-life of the administered EVs and investigate their degradation may be needed. For all the animal studies, sample size should be large enough to allow for a scientific interpretation of test results, and appropriate controls must be included.

4.2 Toxicity Data

4.2.1 Single/Repeat-Dose Toxicity

For the toxicity assessment of EV therapy products, dose-escalation studies should be conducted in appropriate animal species. If the test results indicate immune system abnormalities in the animal model, immunotoxicology studies are necessary.

4.2.2 Gentoxicity

Since EVs carry a variety of heterogeneous cargos that encompass proteins, lipids, and nucleic acids, they might induce genetic or chromosomal aberrations. Analysis of the profile of EV cargos may contribute to predicting the genotoxicity of the EVs. Considering their characteristics, genotoxicity studies should be conducted in compliance with Regulation on Toxicity Studies of Medicinal Products.

4.2.3 Tumorigenicity/Carcinogenicity

As EVs do not contain (stem) cells, tumorigenicity/carcinogenicity studies are not generally required. Nonetheless, for immortalized cells or transgenic cells, oncogenes or oncoproteins may possibly be present in

the EVs, and, consequently, tumorigenicity/carcinogenicity studies may be warranted depending on the cell type of origin and the transgene used. Besides, if tumorigenicity/carcinogenicity studies are deemed necessary considering the repeat-dose toxicity data or the duration of administration in clinical settings, these studies can be performed.

4.2.4 Immunogenicity

In general, as the potential of EVs to induce immunogenicity cannot be ruled out, immunogenicity studies should be carried out. It has been reported that undesirable immune responses could increase in recipients of EV therapy products when animal-derived materials such as fetal bovine serum (FBS) were used during manufacturing. In addition, when EVs are produced using genetically modified cells, the possible resultant immunogenicity should be considered.

5. Clinical Considerations for EV Therapy Products

Unlike cell therapy products, cells are excluded from EV therapy products; therefore, the existing criteria and methodologies used for clinical studies of drug products are also applicable to clinical investigations of EV therapy products.

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