الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

# Guidance on Submission of Chemistry, Manufacturing, and Control (CMC) Information for Cell-based Clinical Trial Applications

***Adopted from The US Food and Drug Administration and The European Medicines Agency and edited by SFDA***

**Version 1.0**

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# Guidance on Submission of Chemistry, Manufacturing, and Control (CMC) Information for Cell-based Clinical Trial Applications

**Version 1.0**

Saudi Food & Drug Authority

Drug Sector

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**Saudi Food and Drug Authority**

**Vision and Mission**

## Vision

To be a leading international science-based regulator to protect and promote public health

## Mission

Protecting the community through regulations and effective controls to ensure the safety of food, drugs, medical devices, cosmetics, pesticides and feed

## Document Control

| Version | Adopted by | Date | Comments |
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# I. INTRODUCTION

This guideline addresses the specific documentation requirements for evaluation of Chemistry, Manufacturing, and Control Information parts in Investigational New Drug Applications (INDs) submitted to the Saudi Food and Drug Authority.

The requirements defined in this guideline are sourced from the following adopted guidelines:

- The FDA Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs), and
- The EMA Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials.

The objective of this document is to address the quality requirements of an investigational medicinal product for a given clinical trial and not to provide guidance on a Company's overall development strategy for a medicinal product.

# II. APPLICATION CONTENT

CMC part of the IND should be provided in a Common Technical Document CTD format of Module 3 and include the most up-to-date available information/requirements.

The IND submission should contain the following sections, if appropriate:

1. Characterization of Investigational Product
2. Product manufacturing - Raw Materials and Components
3. Product Manufacturing - Process Description
4. Analytical Testing of Investigational Product
5. Release Criteria of Investigational Product
6. Stability of Investigational Product
7. Other issues

## 1. Characterization of Investigational Product

This section should include an introduction to cell-based product being investigated, including a description of its active ingredient(s), mode of action, and proposed clinical use.

### 1.1.Nomenclature

Information concerning the nomenclature of the active substance. For example, recommended International Non-Proprietary Name (INN) if assigned.

### 1.2.Structure

A brief description of the predicted structure should be provided.

### 1.3.General properties

The proposed mechanism of action should be explained as well as physiochemical properties such as biological activity (ability or capacity of a product to achieve a defined biological effect).

## 2. Product Manufacturing - Raw Materials and Components

A list of all materials and components used in manufacturing of your product and the testing performed must be included. The sections below detail the information on manufacturing components that we recommend you submit in an IND.

### 2.1.Cells

2.1.1. Allogeneic and/or Autologous Cell Components

- Cell source: tissue and cell type (e.g., colon, hematopoietic, neuronal, T cells).
- Mobilization protocol: whether donor cells are activated ex vivo or activated in vivo in the donor.
- Collection or recovery method: state the procedure used to obtain cells (e.g., leukapheresis indicating the device used if possible), the name and location of the GMP certified health care collection facility, and transport conditions if shipped to a processing facility for further manufacturing.
- Donor screening and testing: the donor screening and testing that is performed to determine donor eligibility.

a) Autologous

No donor eligibility screening for cells and tissues for autologous use is required, however, determination of risk of propagation of pathogens from manufacturing procedures should be evaluated, and precautions to prevent the spread of viruses or other adventitious agents to persons other than the autologous recipient should be described

b) Allogeneic

Donor eligibility screening and testing is required. Manufacturing procedures should insure that there is no risk of spread of pathogenic agents that may be present in the donor. In addition, precautions to prevent the spread of viruses or other adventitious agents to other persons should be described. Donors of all types of cells and tissues must be screened and tested (Table 1). Documentation on the use of commercially available test kits in detection assays and documentations of these tests is required. Typing for polymorphisms, human leukocyte antigen (HLA) matching, and cord blood testing should be considered as appropriate.

Table 1:

| | **Autologous** | **Allogeneic** |
|---|---|---|
| Donor screening and testing | Not required | Required |
| List of tests | - | HIV-1, HIV-2, hepatitis B virus (HBV, surface and core antigen), hepatitis C virus (HCV), Treponema pallidum (syphilis), and malaria |
| Testing for Donors of viable leukocyte-rich cells or tissues | - | (HTLV-1, HTLV-2) and CMV |
| If cord blood other maternally derived tissue | - | Describe testing and screening performed on birth mothers. |

### 2.1.2. Cell Bank System

Information relating to the cell bank system (i.e., master cell bank (MCB), and working cell bank (WCB)) used in product manufacture should be described. In addition, you should describe the history, source, derivation, characterization of each cell bank (both MCB and WCB), and the frequency at which testing is performed should be stated.

a) Master Cell Bank (MCB)

Information regarding MCB history, source, derivation and characterization, including testing to adequately establish the safety, identity, purity, and stability of the cells such as:

- Product microbiologic characteristics: including sterility, mycoplasma, in vivo and in vitro testing for adventitious viral agents, as appropriate.
- Freedom from the presence of specific pathogens: including, for human cells, testing for CMV, HIV-1 & 2, HTLV-1 & 2, EBV, B19, HBV, and HCV, as appropriate. For cell lines that are exposed to bovine or porcine components (e.g., serum, serum components, trypsin), appropriate testing would include testing for bovine and/or porcine adventitious agents.
- Identity of the cells: including tests to distinguish the specified cells through physical or chemical characteristics of the cell line (i.e., phenotype, genotype, or other markers).
- Purity of bank cells, including identification and quantification of any contaminating cells.
- Testing for activity of cells: (e.g., activated lymphocytes, dopamine secretion, insulin secretion) and cell maturation (e.g., dendritic cells). This should be performed if activity is relevant to the therapeutic nature of the product.
- Processes critical to product safety: as applicable, including:
    - Culture conditions used, including documentation of all media, and reagents/components used during production, with copies of relevant certificates of analysis (COA).
    - Cryopreservation, storage, and recovery of the MCB, including information pertaining to cell density, number of vials frozen, storage temperature, and cell bank location.
    - Genetic and phenotypic stability of the MCB after multiple passages as well as viability of cells after cryopreservation.

b) Working Cell Bank (WCB)

If there is a two-tiered cell bank system in place (MCB and WCB), we recommend that you test the WCB for the following: In vitro adventitious viral agent testing; Bacterial and fungal sterility; Mycoplasma; and Limited identity testing (e.g., Southern blot, flow cytometry).

### 2.2.Reagents

Reagents or materials that are used for cellular growth, differentiation, selection, purification, or other critical manufacturing steps but are not intended to be part of the final product must be listed in your IND. These reagents can affect the safety, potency, and purity of the final product, especially by introducing adventitious agents.

- Examples include fetal bovine serum, trypsin, digestion enzymes (e.g., collagenase, DNAse) growth factors, cytokines, monoclonal antibodies, antibiotics, cell separation devices, and media and media components.

#### 2.2.1. Tabulation of Reagents Used in Manufacture

The SFDA recommends providing the following information on all reagents used during product manufacturing:

- concentration of the reagent at the manufacturing step at which it is used;
- vendor/supplier;
- Source (Table 2).

Generally, if all animal-derived products are used, the following information in the animal components database should be included; source organism, supplier/vendor, country of origin, and stage of manufacture.

#### 2.2.2. Qualification

If the reagent is not FDA-approved or clinical grade reagents, we recommend performing a sufficient testing to ensure quality and safety of reagents, with providing characterization data or certificate of analysis.

### 2.2.3. Determination of Removal of Reagents from Final Product

Description of procedures that have been employed to remove or eliminate residuals of reagents, in which the cell product should be tested for residual manufacturing reagents with known or potential toxicities with description of test procedures used to detect residual levels of these reagents, from the final product at acceptable levels, with providing supporting characterization data.

Table.2

| Source | Requirements |
|---|---|
| Human | a. For human AB serum, it should be obtained from an approved blood bank and meets all blood donor criteria.<br>b. For all other reagents that are human derived you should identify whether it is a licensed product, and provide a certificate of analysis |
| Porcine | a. If porcine products are used, a certificate of analysis or other documentation that the products are free of porcine parvovirus must be provided. A description and justification of testing methods and the stage at which virus testing is performed should also be included. |
| Bovine | a. If a reagent is derived from bovine material, identify the bovine material, its source, location where the herd was born, raised, and slaughtered as well as TSE certificate for all bovine materials used during the manufacturing process |

2.2.4. Other Concerns

Due to concerns with penicillin allergies, beta-lactam antibiotics should not be used during the manufacturing process. If no substitute is available, a rationale for use of beta lactams and description of precautions to prevent hypersensitivity should be detailed. Appropriate exclusion criteria for the study and proper informed consent to address potential patient sensitivity should be prepared.

### 2.3.Excipients

Excipients are components intended to be part of the final product, such as human serum albumin or Dimethyl Sulfoxide (DMSO). List of all excipients used during manufacture of the product, their concentrations and source should be stated. In addition, if a novel excipient is used, manufacturing and characterization studies must be submitted.

## 3. Product Manufacturing - Process Description

All procedures used during the collection, production, and purification of the cellular therapy product should be included (list or summary). Schematic of the production and purification process parameters and in-process-testing should be given, operating parameters (e.g., process times, temperature ranges, cell passage number, pH, CO2, dissolved O2, glucose level). The control strategy should focus on safety relevant in-process controls (IPCs) and acceptance criteria for critical steps. These in-process controls should be provided with action limits or preliminary acceptance criteria. Batch(es) and scale should be defined, including information on any pooling of harvests or intermediates.

### 3.1.Preparation of Autologous or Allogeneic Cells

3.1.1. Method of Cell Collection/Processing/Culture Conditions

Report volume and number of cells collected, including description of mechanical or enzymatic digestion steps used. The selection or separation device used such as density gradients or magnetic beads should be reported. Description of culture systems whether closed or open should be justified.

3.1.2. Irradiation

If the autologous or allogeneic cell –or feeder layer- product is irradiated before injection, data to demonstrate that the cells are rendered replication- incompetent, but still maintain their desired characteristics after irradiation should be submitted. Information on cell irradiator source should be reported.

3.1.3. Final Harvest

Detailed description of the final harvest. If centrifuged prior to final formulation, describe wash conditions and media used. If a material is to be held for a time period, supporting evidence should be provided for its stability.

### 3.2.Process Timing and Intermediate Storage

The approximate time elapsed for each step from cell collection to final harvest should be reported. This is important to know the time limit of each step-in production to determine what, if any, in-process testing to perform. In addition, you should describe the time and conditions of storage prior to patient administration, including cryopreservation.

### 3.3.Final Formulation

A description of the final formulation of product, including cell density or cell concentration, and excipients such as growth factors or human serum albumin must be described. Vendors and final concentrations of excipients present in final formulation should be reported. Description of logistics involved with product shipment and product-thawing demonstrating consistent should must be illustrated.

## 4. Analytical Testing of Investigational Product

Product testing is an integral part of ensuring control of the manufacturing process and lot-to-lot consistency. The product testing for cellular therapies include, but not be limited to, microbiological testing (including sterility, mycoplasma, and adventitious viral agent testing) to ensure safety and assessments of other product characteristics such as identity, purity (including endotoxin), viability, and potency.

### 4.1.Microbiological Testing

Microbiological tests should be performed on cell banks, in-process intermediates, and the final product, as appropriate.

4.1.1. Sterility testing (bacterial and fungal testing)

a. Sterility methods

Sterility methods used should follow SFDA's approved standards. If another method is to be used, you should describe its suitability.

If the manufacturing process uses antibiotics, they should be removed before sterility testing. If the antibiotics cannot be removed from the final product, appropriate assays should be used to ensure that any residual antibiotic present in the product does not interfere with the results of sterility testing.

b. Test timing

In-process sterility testing should be performed at critical points during manufacturing. You should justify the choice of testing points during manufacturing process. The description of test method and timing must be provided.

If final product is to be stored frozen, sterility testing is to be performed on the product prior to cryopreservation for the sterility results to be available at the time of infusion to the patient. However, if the product undergoes manipulation (e.g., washing, culturing) after thawing, sterility testing must be repeated, and the results of in-process sterility testing should incorporate with the accepted final product release specifications criteria.

If the product is to be administered to the patient before sterility test results of the final product are available, then the below alternate approaches should be performed to provide sterility assurance:

- In-process sterility testing on a sample taken 48 to 72 hours prior to final harvest or after the last re-feeding of the cell cultures
- A rapid microbial detection test such as a Gram stain or other procedure on the final formulated product.

Under this approach, the release criteria for sterility would be based on a negative result of

the Gram stain and a no-growth result from the 48 to 72 hour in-process sterility test.

Although results of 14-day sterility culture testing will not be used for release of the final product, it should be documented. A no-growth result will provide assurance that aseptic technique was maintained. A positive result will provide information for the medical management of the subject, and trigger an investigation of the cause of the sterility failure.

Even after the product has been given to the patient, the sterility culture on the final formulated product and when possible the in-process culture should be continued to obtain the full 14-day sterility test result.

If the 14-day sterility test is to be positive, then the following procedure should be performed:

- The results of investigation of cause and any corrective actions of sterility failure should be reported in an information amendment submitted to your IND in a timely manner, within 30 calendar days after initial receipt of the positive culture test result.
- Evolution of the subject for any signs of infection that may be attributable to the product sterility failure should be evaluated by the investigator. If the patient experiences any serious and unexpected adverse drug experience that could be from administration of the sterility failure of the cellular product, then you must report this information to SFDA in an IND safety report no more than 15 calendar days after your initial receipt of the information.

#### 4.1.2. Mycoplasma

There are several possible sources of mycoplasma contamination. Two major sources include animal serum products used in culture and the culture facility environment, particularly with open culture systems. Mycoplasma testing on the product should be performed at the stage of manufacturing when the test is most likely to detect contamination, such as after pooling of cultures for harvest but prior to cell washing. Testing should be conducted on both cells and supernatant. Due to the limited dating period of many cellular products, it is frequently not feasible to perform the recommended culture-based assay for release testing. In those cases, use of Polymerase Chain Reaction (PCR)-based mycoplasma assays or another rapid detection assay during product development is recommended.

4.1.3. Adventitious Agent Testing

As appropriate, you should perform and describe in your IND adventitious agent testing as set out below.

a. In vitro viral testing

When cell lines are used, the cell lines used must be described and perfume perform in vitro viral testing.

In vitro viral testing should be performed on the MCB, WCB, and as a one-time test on the End of Production (EOP) cells. Testing should be conducted by inoculating the test sample (MCB) onto various susceptible indicator cell lines such as the human cell line MRC-5 or Vero cells, which are primate in origin. The choice of cells used would depend on the species of origin of the product to be tested. An appropriate test should include monolayer cultures of the same species and tissue as that used for production of the product, as well as a human and a non-human primate cell line susceptible to human viruses. In addition, the test should include a measure of both cytopathic and hemadsorbing viruses.

b. In vivo viral testing

When cell lines are used, we recommend that you perform and submit data on in vivo viral assays carried out by inoculating the test sample (MCB) into animals such as adult and suckling mice and embryonated hen eggs. You should consider whether to include additional testing of guinea pigs, rabbits, or monkeys. Such studies would assess the test animals for any indication of illness. If such additional testing is appropriate, you should describe and explain the suitability of the animals used.

c. Selected species-specific testing for adventitious viruses

MCB should be tested for appropriate, species-specific viruses along with a description of the testing that is performed and the different stages of the manufacturing where those tests are performed (e.g., cell banks, final product), and the test methods used.

If human cell lines are used in the therapeutic product, we recommend that you perform testing for human pathogens (CMV, HIV-1 & 2, HTLV-1 & 2, EBV, HBV, HCV, B19), and other human viral agents, as appropriate. You should perfume this testing as these cells are manipulated (cultured for extended time periods) and human pathogens can be introduced or propagated during the extended culture periods. Human viral agents can be investigated using a PCR-based test system.

d. Testing for Retroviruses

It is recommended that you perform testing for replication competent retrovirus (RCR) in the production of retroviral vectors at multiple points in production, including Master Viral Banks (MVB) and Working Viral Banks (WVB).

**4.2.Identity**

Verify identity of the MCB, WCB, and the final product by assays that will identify the product and distinguish it from other products being processed in the same facility. For the final product, identity testing is important to ensure that the contents of the vial are labeled appropriately.

If the final product consists of one or more cell lines, we recommend that you establish identity tests and/or controls that distinguish between the multiple cell lines used, and describe those tests and/or controls. Tests may include assays for cell surface markers or genetic polymorphisms.

**4.3.Purity**

Product purity is defined as relative freedom from extraneous material in the finished product, whether or not harmful to the recipient or deleterious to the product. Purity testing includes assays for pyrogenicity/endotoxin, residual proteins or peptides used to stimulate or pulse cells, reagents/components used during manufacture, such as cytokines, growth factors, antibodies, and serum, and unintended cellular phenotypes.

4.3.1. Residual Contaminants

The appropriate purity testing should include assays for residual peptides, and proteins used during production and purification, and reagents used during manufacture, such as cytokines, growth factors, antibodies, beads, and serum.

Appropriate purity testing should include a measurement of contaminating cell types or cell debris.

4.3.2. Pyrogenicity/Endotoxin

The rabbit pyrogen test method is the currently required method for testing biological products for pyrogenic substances. Although the pyrogenicity test is required, there may be specific cases where this test method cannot be performed for release due to properties of the cellular product (i.e., short product shelf life, toxicity of product in rabbits). Under these circumstances, a test method such as the Limulus Amebocyte Lysate test method (LAL) may be used as an alternative method, but prior to licensure must be shown to provide equal or greater assurances of safety, purity, and potency.

Recommended upper limit of acceptance criterion for endotoxin be 5 EU/kg body weight/hour. For intrathecally-administered drugs, an upper limit of acceptance criterion of 0.2 EU/kg body weight/hour is proposed. You should describe in your IND the pyrogenicity/endotoxin testing you conduct, and your acceptance criterion for release.

**4.4.Potency**

Description and justification of all assays you will use to measure potency. They should be quantitative in nature, and include a qualitative biological assay. Potency assay consists of in vivo or in vitro tests that measure an appropriate biological activity. If development of a quantitative biological assay is not possible, then a quantitative physical assay, which correlates with and is used in conjunction with a qualitative biological assay, can be used.

**4.5.Other**

4.5.1. Viability

Minimum release criteria for viability should be established. For somatic cellular therapies, the minimum acceptable viability specification is generally set at 70 percent. If this level cannot be achieved, data to support of a lower viability specification, demonstrating, for example, that dead cells and cell debris do not affect the safe administration of the product and/or the therapeutic effect should be submitted.

4.5.2. Cell Number/Dose

Specifications for the minimum number of viable and functional cells as part of product testing and release should be set. The basis for maximum number/dose of cells to be administered should be explained.

## 5. Release Criteria of Investigational Product

The final product is the final formulated product used for administration to human subjects. Each lot of product manufactured should be tested for final product release criteria. In some cases, each dose may be considered a single lot, depending on the manufacturing process. Prior to the administration to human subject, the results from the final product release criteria testing should be available. In cases where the results of one or more release criteria are not available at the time of product release, it is recommended that the investigator indicate this situation in the IND and provide a clear reporting plan if the acceptance criteria are not met. In tabular format, list all proposed specifications (tests for safety, purity, potency, and identity, test methods, and acceptance criteria), including test sensitivity and specificity, where appropriate, for the final product.

## 6. Stability of Investigational Product

Stability testing must be performed to establish that the product is sufficiently stable for the time of study both chemically and physically in all phases of the IND. A stability protocol and data for both in-process material and the final cellular product must be submitted. A proposed stability protocol should include a measure of product sterility, identity, purity, quality, and potency. For each test conducted, test method, sampling time points (there should be a zero-time point), testing temperature, and other appropriate information, including justification of the assays used to indicate product stability, measuring those parameters for the duration of storage is detailed. We recommend sterility testing be performed at zero-time, end of stability study, and at an intermediate point during the study.

### 6.1. In-Process Stability Testing

If cells are cryopreserved, stability protocol used to ensure that the product is stable during the period of cryopreservation should be reported. A comparison of analyses

carried out pre-freeze and post-thaw should be conducted. Any stability testing performed on the product during the holding steps, such as cryopreservation of cells and storage of bulk product should be described.

### 6.2.Final Product Stability Testing

Data that demonstrate that the product is stable between the time of product formulation and infusion to subjects to aid in establishing an expiration-dating period. Testing should be performed at the appropriate temperatures and at time points consistent with predicted storage times. If the product is shipped from the manufacturing site to the clinical site, description of the time and shipping conditions (e.g., packaging, temperature) should be given. The stability protocol should also be adequate to demonstrate that product integrity, sterility, and potency are maintained under the proposed shipping conditions.

## 7. Other Issues

### 7.1. Product Tracking

A tracking system should be established and described in the IND. This should identify the chain of custody of the product from the time of collection of the raw/starting material to the administration of the final therapeutic product to the subject.

### 7.2. Labeling

Labelling protocols should be established and followed throughout the manufacturing process. The IND should include a description of the labeling protocol. It is recommended that the label on the product contain patient's information (non-personal patient identifiers), considering their confidentiality, the date of product manufacture, storage conditions, expiration date and, product name.

### 7.3. Container/Closure

Container type and closure used, and their compatibility with the product should be studied and data presented.

### 7.4. Validation and Qualification of the Manufacturing Process

Quality control of the reagents and material that are used in the manufacturing process should be implemented to ensure the patients safety, preventing the transmission of adventitious infectious agent, and to guarantee the final product's purity and potency. The Quality Control (QC) plan is need to be established and documented. It is designed to prevent, detect, and correct deficiencies that may compromise product integrity or function, or that may lead to the possible transmission of adventitious infectious agents. Establishment and implementation of written procedures to ensure proper manufacturing oversight is mandatory. This includes the responsibilities and procedures applicable to the quality control unit. A designated QC independent specialist are recommended. They are responsible to evaluate the effective of the QC activities and to develop and conduct audit protocols**.**

Below are some of the functions to be included in a QC plan:

- Responsibility for examining the various components used in the production of a product (e.g., containers, closures, in-process materials) to ensure that they are appropriate and meet defined, relevant quality standards
- Responsibility for review and approval of production procedures, testing procedures and acceptance criteria
- Responsibility for releasing or rejecting each clinical batch based on a cumulative review of completed production records and other relevant information and
- Responsibility for investigating and initiating corrective actions if unexpected results or errors occur during production.