Safety Testing of Human Allogeneic Cells Expanded for Use in Cell-Based Medical Products

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Draft Guidance for Industry

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

Allogeneic cells of human origin may be expanded in culture to manufacture medical products consisting of live cells, inactivated cells, cell lysates, or other cell-based materials such as cell-derived particles. We, FDA, are providing you, sponsors of allogeneic cell-based medical products, recommendations for determining the appropriate cell safety testing to support an Investigational New Drug Application (IND)[1] or a Biologics License Application (BLA).[2] Cell safety testing should be based on a risk analysis that considers the expansion potential of the cells, the reagents that are used to expand the cells in culture, and the number of individuals the cell-based medical product is capable of treating.[3, 4]

This guidance supplements the following two final guidances:

- "Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs); Guidance for Industry," dated January 2020[5], and
- "Guidance for FDA Reviewers and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs)," dated April 2008.[6]

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[1] See generally 21 CFR part 312.
[2] See generally 21 CFR part 601.
[3] Depending on the stage of development, this may be the number of subjects to which the investigational product is capable of being administered in clinical investigations or the number of patients the product is capable of treating following licensure.
[4] This guidance does not address the measurement or analysis of cell characteristics that may be relevant to biological activity.
[5] https://www.fda.gov/media/113760/download.
[6] https://www.fda.gov/media/73624/download.

In general, FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. SCOPE

This guidance applies to allogeneic cell-based products that are regulated by the Office of Therapeutic Products of the Center for Biologics Evaluation and Research (CBER) under section 351 of the Public Health Service Act (42 U.S.C. 262). This guidance applies to cultured allogeneic cells, including cell banks[7], that are sources of the intended constituents of the final drug product, as well as combination products that contain an allogeneic cell or cell-based biologic constituent part in combination with a drug and/or device. The recommendations in this guidance also apply to genetically modified allogeneic cells that have been transduced with viral and/or plasmid vectors, and cells that have undergone genome editing. This guidance does not apply to cell substrates that are used during manufacturing of non-cell-based products such as viruses, gene therapy vectors, or recombinant proteins.[8] Recommendations for feeder or other cells used as reagents during manufacturing are beyond the scope of this guidance.[9]

III. BACKGROUND

Viral and microbial contamination is a potential risk for all cell-based medical products, especially when the cells are cultured extensively during manufacturing. Contamination may be present in the source cells, or the cells may become contaminated with adventitious agents during manufacturing. In addition, genomic changes that result in tumorigenic cells can occur during extensive culture.

Under Title 21 of the Code of Federal Regulations (CFR), 610.18(c)(1), "Cell lines used for manufacturing biological products shall be:

(i) Identified by history;

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[7] For the purpose of this guidance, cell bank refers to cells of uniform composition that are stored for further manufacturing.

[8] The recommendations in this guidance do not apply to products reviewed by CBER's Office of Vaccine Research and Review or Office of Blood Research and Review, or by the Center for Drug Evaluation and Research or the Center for Devices and Radiological Health.

[9] Refer to the FDA draft guidance entitled "Considerations for the Use of Human- and Animal-Derived Materials and Components in the Manufacture of Cell and Gene Therapy and Tissue-Engineered Medical Products; Draft Guidance for Industry" dated April 2024 for recommendations on safety testing of feeder cells. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-use-human-and-animal-derived-materials-manufacture-cell-and-gene-therapy-and-tissue. When finalized, this guidance will represent FDA's current thinking on the topic.

(ii) Described with respect to cytogenetic characteristics and tumorigenicity;
(iii) Characterized with respect to in vitro growth characteristics and life potential; and
(iv) Tested for the presence of detectable microbial agents."

In addition, 21 CFR 312.23(a)(7)(i) requires an IND to include sufficient information to assure the proper identification, quality, purity, and strength of the investigational product. An IND is also specifically required to include a description of the acceptable limits and analytical methods used to assure, among other things, the purity and quality of both the drug substance (DS) and drug product (DP), 21 CFR 312.23(a)(7)(iv)(a)-(b). Potential impurities for cell-based medical products include contamination with viruses or bacteria. Genomic integrity and in vitro growth characteristics are factors that affect the quality of cell-based medical products used under INDs and thus should be evaluated. FDA may place an IND on clinical hold if the IND does not contain sufficient CMC information required under 21 CFR 312.23 "to assess the risks to subjects of the proposed studies" (21 CFR 312.42(b)(1)(iv) and (b)(2)(i)) or if the CMC information indicates that the "[h]uman subjects are or would be exposed to an unreasonable and significant risk of illness or injury" (21 CFR 312.42(b)(1)(i) and (b)(2)(i)).

The purpose of this document is to provide guidance on safety testing to assist manufacturers in addressing the requirements of 21 CFR 610.18(c)(1), 21 CFR 312.23(a)(7), and other relevant regulations, as applicable, with respect to human allogeneic cells expanded for use in cell-based medical products. FDA's recommendations for cell safety testing reflect a risk-based approach that takes into consideration both the specific characteristics of the cells and their proposed use.

We recommend that you provide an integrated assessment of the risk of potential contamination with adventitious agents in the electronic Common Technical Document (eCTD) section 3.2.A.2 (Adventitious Agents Safety Evaluation) of your IND or BLA submission (Ref. 1).[10] We also recommend that this section describe risk mitigation measures, including information on the selection, testing, and safety assessment of cells and cell banks.

IV. CONSIDERATIONS FOR CELL SAFETY TESTING

For allogeneic cells, donor screening and testing must be performed as required in 21 CFR part 1271, subpart C, except for those cells that meet the exceptions in 21 CFR 1271.90(a).[11] The donor screening and testing information should be provided in the IND or BLA submission.

In an IND, you must provide a list of all materials used in manufacturing, including the quality or grade of these materials (see 21 CFR 312.23(a)(7)(iv)(b)), which assists FDA in determining if the proposed cell safety testing is adequate to assure the safety of the investigational product.

[10] For information on the submission of an eCTD, see the FDA website https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/electronic-common-technical-document-ectd.
[11] For more information regarding these requirements, see Testing Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/P): Specific Requirements, https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/testing-donors-human-cells-tissues-and-cellular-and-tissue-based-products-hctp-specific-requirements.

Information describing the source of each reagent and its components, along with a Certificate of Analysis, should be submitted within IND. The origin of animal- and human-derived reagents used in the manufacturing process, and the acceptance criteria for these reagents, will influence the appropriate amount and types of safety testing.[12]

The nature and extent of cell safety testing needed to provide adequate assurance of product safety will generally depend on the expansion potential of the cells and the number of individuals the cell-based medical product is capable of treating. A description of the culture methods used to expand the cells to manufacture the allogeneic cell-based medical product should be provided in the IND or BLA submission. This information should include the expansion potential of the cells, the passage number that is intended to be used to make the allogeneic cell-based medical product and cell storage conditions.

A. Continuous Cell Lines

Cellular products may be produced from continuous cell lines, including induced pluripotent stem cells, embryonic stem cells, cancer cell lines, and transformed cell lines. The manufacturing process for a cellular product made from continuous cell lines usually includes the creation of a cell bank to ensure a consistent source material for the manufacture of the cell-based product.

Cell banks made from continuous cell lines should be tested for adventitious viruses and undergo additional safety evaluations as outlined in section V of this guidance.

B. Primary Cells

1. Primary Cells Capable of Extensive Expansion in Culture

If allogeneic primary cells from a single donor can be expanded in culture to a cell number that is sufficient to be administered to many individuals, then we recommend conducting the cell safety testing described in section V of this guidance. This testing should generally be performed on a cryopreserved cell bank. However, some manufacturers of cell-based medical products do not use a cell bank during manufacturing. Instead, they expand the cells extensively and then store them as a cryopreserved lot of drug substance or final product. In this case, the cell safety testing outlined in section V of this guidance should be done on the lot of cryopreserved cells.

2. Primary Cells Capable of Limited Expansion in Culture

[12] Refer to the FDA draft guidance entitled "Considerations for the Use of Human- and Animal-Derived Materials and Components in the Manufacture of Cell and Gene Therapy and Tissue-Engineered Medical Products; Draft Guidance for Industry" dated April 2024 for additional information regarding human- and animal-derived reagents. When finalized, this guidance will represent FDA's current thinking on the topic.

Primary cells with a limited expansion potential can be expanded to make a cellular therapy product, or to create small to midsize cell banks or a single lot of cells to manufacture cell-based products capable of being administered to a limited number of individuals. In these situations, the complete list of cell safety testing outlined in section V of this guidance is not recommended because full adventitious virus testing is generally not feasible to perform on a small lot of cells or final product. Instead, an abbreviated test matrix, as outlined in section VI of this guidance, is recommended.

C. Cells That Are Administered To A Few Individuals Or A Single Individual

Primary cell cultures that are not subcultivated or primary cell cultures that are subsequently subcultivated for only a very limited number of population doublings are not subject to the provisions in 21 CFR 610.18(c) for cell lines used for manufacturing biological products (21 CFR 610.18(c)(3)). It is not recommended that primary allogeneic cells that are minimally expanded in culture to be administered to only a few individuals, or a single individual, undergo cytogenetic analysis or adventitious virus testing. However, these cells must still be tested for sterility (21 CFR 610.12), purity (e.g., endotoxin) (21 CFR 610.13), as required for lot release of licensed cellular products (21 CFR 610.1). Note that if there are specific safety concerns regarding reagents used during product manufacturing, then adventitious virus testing may need to be performed on the reagents of concern to assure product safety. For example, there may be a safety concern due to the use of animal and human derived reagents because they have the potential to introduce adventitious agents to the cell-based medical product.

V. TESTING RECOMMENDATIONS FOR HIGHLY EXPANDED CELLS

This section contains recommendations for testing cell banks of highly expanded primary cells, and cell banks made from continuous cell lines, including pluripotent stem cells, cancer cells, and transformed cells.

Cell-based medical products may use a one-tier or two-tier cell banking system. A one-tier system consists of a master cell bank (MCB) only, while in a two-tier system there is also at least one working cell bank (WCB) derived from the MCB.

Some manufacturing schemes may use multiple levels of cell banks; however, it may not be necessary to test all the cell banks for safety as outlined below. For instance, cells used as the cellular starting material for genetically engineered stem cells may be banked but would not be considered the MCB. Instead, the cell bank of genetically modified stem cells would generally be considered the MCB, and the cell safety testing described below should be performed on those genetically modified cells since there is potential for adventitious agent contamination during the genetic modification. Likewise, if donor cells used as starting material for a cell-based product are banked prior to extensive expansion in culture, the highly expanded cells should be considered the MCB and should be used for the safety testing outlined below.

Some cell-based medical products do not use a cell bank during manufacturing but may store the final product as a single lot of highly expanded cryopreserved cells that could be used to treat many individuals. In this case, the MCB cell safety testing outlined below should be performed on the lot of cryopreserved cells.

A. Master Cell Bank

FDA makes the recommendations below regarding safety testing for an MCB. (We note that, for licensure, testing must comply with the general biological products standards in 21 CFR Part 610).

- Sterility testing – Testing for bacterial and fungal sterility may be performed in accordance with United States Pharmacopeia (USP)<71> or using another appropriately qualified and validated method (see 21 CFR 610.12).

- Mycoplasma testing – Mycoplasma testing can consist of culture-based methods per USP<63>. Alternative assays may be used to detect mycoplasma, but such an assay should be shown to have sensitivity that is comparable to the compendial method.

- Human pathogen testing using polymerase chain reaction (PCR) may include testing for human immunodeficiency virus (HIV) -1 &2, human T cell lymphotropic virus (HTLV) 1 & -2, hepatitis viruses B and C, cytomegalovirus (CMV), Epstein-Barr virus (EBV), human parvovirus B19, human papillomavirus (HPV), human herpes viruses (HHV) -6, -7, and 8, John Cunningham (JC) virus, and BK virus, as appropriate. FDA should be consulted for application-specific testing recommendations when cells will be used in immunocompromised individuals.

- In vitro adventitious virus testing – Three cell lines should generally be used: human diploid (e.g., MRC5 cells), monkey kidney (e.g., Vero cells), and another cell line of the same species and tissue type as that used for production (e.g., HeLa cells if the product was made using human cells). However, different cell lines may be appropriate depending on the manufacturing process. For instance, when insect cells are used during manufacturing, BHK21 cells may be used to detect viruses such as rhabdoviruses. In this example, testing for adventitious viruses using BHK21 cells would address the recommendation of testing for viruses in cells of the same species in which product production occurs. The BHK21 cells would be the third cell line recommended for adventitious virus testing when used in addition to the human diploid and monkey kidney cell lines.

- In vivo adventitious virus testing is recommended when cells have specific risk factors that are not fully mitigated by other types of testing. Examples of such risk factors include, contact with animals or animal cells, use of animal

or human derived reagents that do not have sufficient safety information, use of cells from unknown sources, and insufficient information on cell culture history and methods. In vivo adventitious virus testing consists of inoculation of adult and suckling mice, and embryonated chicken eggs with cells. Alternatively, a high throughput sequencing method may be used instead of in vivo adventitious virus testing to detect contaminating viruses. However, if a high throughput sequencing method such as next generation sequencing is used, we recommend that you include a description of any qualification or validation studies performed in your regulatory submission. We strongly recommend that if a high throughput sequencing method is used for adventitious virus testing, the proposed method and validation study plan be discussed with FDA prior to implementation.

- Transmission electron microscopy should be performed to detect virus particles.

- Retroviral testing – If the human sourced cells used to make the cell-based medical product are grown on feeder layers of non-human cells, these human cells should be evaluated for the presence of species-specific and endogenous retrovirus.

- Species-specific virus testing should be performed. If human sourced cells contact rodent cells or rodent-derived reagents during manufacturing, then testing for mouse/rat/hamster viruses should be performed. Likewise, if the human sourced cells contact simian or insect cells or reagents, then testing for simian or insect viruses should be performed.

- Testing for animal viruses consistent with the testing described in 9 CFR 113.53 (Requirements for ingredients of animal origin used for production of biologics) and 9 CFR 113.47 (Detection of extraneous viruses by the fluorescent antibody technique) should be performed if animal-derived reagents are used during manufacturing of the cell-based medical product.

    - Testing consistent with 9 CFR 113.47 should be performed for bovine derived viruses listed in 113.47(b)(1) and (2), if bovine-derived reagents are used. Note that bovine-derived reagents should be obtained from sources that minimize the risk of transmissible spongiform encephalopathy.

    - Testing for porcine-derived viruses consistent with the testing described in 9 CFR 113.53(d) and 9 CFR 113.47(b)(1) and (6) should be performed if porcine-derived reagents are used.

    - It may be acceptable to reduce or eliminate testing of the human-sourced cells for animal viruses if the reagent manufacturer

performs and documents adventitious agent testing for the animal-derived reagents consistent with 9 CFR 113.53 and 9 CFR 113.47. Reagent testing documentation should be submitted in the IND or BLA submission.

- Testing for the presence of residual viral and plasmid reprogramming vectors used in the creation of induced pluripotent cell lines should be performed on either the cell bank, drug substance, or final product. An acceptance criterion with justification for acceptable levels of residual programming vectors should be established.

- If a retroviral vector is used to induce gene editing, then the cells used to make the allogeneic cell-based medical product should be tested for the presence of replication competent retrovirus as recommended in the FDA guidance titled "Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up; Guidance for Industry" dated January 2020 (Ref. 2).

- Whole genome sequencing and analysis should be performed on cell banks of continuous cell lines and genome edited cells.

    - Cell lines that are cultured extensively often accumulate mutations during cell expansion. Mutations in protooncogenes, such as p53, are of particular concern. Therefore, we recommend that continuous cell lines that contribute cells to the final product be evaluated by performing whole genome sequencing. The whole genome sequencing method used should have a read depth of at least 50X, and at a minimum, the results should be compared to a database of cancer associated mutations. Justification should be provided for the sequencing method, read depth, and for conclusions related to the safety of the product.

    - For highly expanded clones of genetically modified cells, whole genome sequencing with at least 50X read depth should be performed to identify off-target genome editing, on-target editing outcomes, vector integration events, and to screen for any mutations of concern.

- Cytogenetic testing or whole genome sequencing should be performed on highly expanded primary cells that contribute cells to the final product. Whole genome sequencing as described above is the recommended method of testing genome integrity. Alternatively, if cytogenetic testing is performed, G-banding analysis or other sensitive methods should be used to confirm the cells have a normal karyotype. The karyotypes of at least 20 cells should be analyzed. An acceptance criterion for cytogenetic test results

with justification for discrepancies should be established. Cytogenetic testing is not recommended for continuous cell lines or highly expanded genetically modified cells that have been subjected to whole genome sequencing as recommended above.

- Cytogenetic testing is not recommended for cells that are only used as sources for products such as cell-derived particles and are not present in the final product. Cytogenetic testing is not recommended for irradiated cells used during manufacturing or that are a part of the final product.

- Tumorigenicity testing, highly expanded cells – Under 21 CFR 610.18(c)(1)(ii), cell lines used for manufacturing biological products shall be described with respect to tumorigenicity.

    - In cases where the cells present in the final product are phenotypically similar to those in the MCB, the tumorigenic potential of a product may be tested using cells from the MCB. However, tumorigenicity testing may not be necessary if the cells in the MCB are demonstrated to be comparable to cells that were evaluated and tested for tumorigenicity in preclinical studies. Comparability can be evaluated by measuring product specific characteristics that are associated with product performance and safety.

    - Tumorigenicity testing, continuous cell lines – Genomic stability and growth characteristics should be evaluated, but cancer cell lines and pluripotent cell lines are generally not tested for tumorigenicity as part of cell safety testing since these cell types are expected to be capable of forming tumors.

    - Tumorigenicity testing, irradiated cells – Tumorigenicity testing of irradiated cells is not recommended.

For detailed information on adventitious virus testing, please refer to section IV.A of the guidance "Guidance for Industry: Characterization and Qualification of Cell Substrates and Other Biological Materials Used in the Production of Viral Vaccines for Infectious Disease Indications," dated February 2010 (Ref. 3). Sponsors who intend to use novel analytical technology for adventitious agent evaluation of their product should discuss their proposed approach with FDA during the development of the assay.

B. Working Cell Bank

In some cases, the cells from an MCB may be expanded further into WCBs. WCB testing should include, but not be limited to, sterility, mycoplasma, identity, and in vitro adventitious agent tests described in section V.A of this guidance.

VI. TESTING RECOMMENDATIONS FOR CELLS WITH LIMITED EXPANSION POTENTIAL

As discussed in section IV.B.2 of this guidance, it is generally unnecessary for primary cells that cannot be expanded in culture extensively to undergo all the testing listed in section V of this guidance, unless there are specific safety concerns that such testing would address.

Cell banks or product lots made from cells with limited expansion capability should be tested using an abbreviated cell safety test matrix consisting of:

- Sterility testing;
- Mycoplasma testing;
- Human pathogen testing using PCR, as described in section V of this guidance; and
- In vitro adventitious virus testing as described in section V of this guidance.

Additional safety testing for cells that come in contact with animal-derived reagents during manufacturing, as described in section V of this guidance, may be appropriate.

Genome edited cells that are not extensively expanded in culture should undergo targeted sequencing to assess the frequency of editing at confirmed off-target sites and to ensure the desired on-target editing outcome has occurred. If a retroviral vector is used to induce gene editing, then the cells used to make the allogeneic cell-based medical product should be tested for the presence of replication competent retrovirus (Ref. 2).

If there is a concern that even a limited amount of adventitious virus testing will consume too large a portion of the cellular material available, then testing may be performed on end of production material. The end of production material may be generated by expanding cells from a product lot or a cell bank to a number of cells that is sufficient for the abbreviated cell safety test matrix outlined above in this section.

Table 1. Cell Safety Testing Recommendations for Allogeneic Cells Expanded for Use in Cell-Based Medical Products

Cell description	Cell culture and preparation	Cells that should be tested	Product Use	Cell safety testing recommended
Embryonic stem cells and allogeneic induced pluripotent cells	Cells are expanded into an MCB and WCBs. WCBs are differentiated into final cellular therapy product.	MCB and WCBs	Potentially, many individuals	The MCB and WCBs should be tested as outlined in section V of this guidance
Immortal cancer cell lines and transformed cell lines	Cells are expanded into an MCB and WCBs. Cell-based product is derived from WCBs.	MCB and WCBs	Potentially, many individuals	The MCB and WCBs should be tested as outlined in section V of this guidance
Primary allogeneic cells capable of extensive expansion (highly expanded)	Cells are expanded to make an MCB. MCB vials are thawed and further expanded to make final product.	MCB and WCBs (if one is made)	Potentially, many individuals	The MCB and WCBs (if one is made) should be tested as outlined in section V of this guidance
Primary allogeneic cells, including some genetically engineered cells, capable of limited expansion before loss of cell quality	Cells are expanded several passages to make a small to midsized MCB or a single lot of cells that is used as the cellular therapy product.	MCB or lot of expanded cells, or end of production cells	Limited number of individuals	MCB or lot of expanded cells, or end of production cells should be tested as outlined in section VI of this guidance
Primary allogeneic cells expanded in culture to make a product for a few subjects or a single subject	Cells are expanded to make product lots of cells capable of being administered to a few subjects or a single subject.	The lot of expanded cells	A few individuals or a single individual	Sterility, mycoplasma, and endotoxin testing

VIII. REFERENCES

1. Guidance for Industry: M4Q: The CTD – Quality, August 2001. https://www.fda.gov/media/71581/download.

2. Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up; Guidance for Industry, January 2020. https://www.fda.gov/media/113790/download.

3. Guidance for Industry: Characterization and Qualification of Cell Substrates and Other Biological Starting Materials Used in the Production of Viral Vaccines for Infectious Disease Indications, February 2010. https://www.fda.gov/media/78428/download.