Considerations for the Use of Human- and Animal-Derived Materials in the Manufacture of Cellular and Gene Therapy and Tissue-Engineered 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Draft Guidance for Industry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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Draft Guidance for Industry

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

The use of human- and animal-derived materials[1] to manufacture cellular and gene therapy (CGT) products and tissue-engineered medical products (TEMPs) raises several key issues to consider, including transmission of adventitious agents, material lot-to-lot consistency, and material identity, as well as general material qualification considerations. We, FDA, are providing you, manufacturers of CGT and TEMP products, with recommendations regarding assuring the safety, quality, and identity of materials of human and animal origin used in the manufacture of these products. In addition, recommendations are provided regarding the chemistry, manufacturing, and control (CMC) information submitted in an investigational new drug application (IND) relating to the use of human- and animal-derived materials.

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 (Gene Therapy CMC Guidance) (Ref. 2) 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 (Cell Therapy CMC Guidance) (Ref. 3).

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

[1] As defined in "Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients; Guidance for Industry," (September 2016) (Ref. 1), "material" is a general term used to denote raw materials (starting materials, reagents, solvents), process aids, intermediates, active pharmaceutical ingredients, and packaging and labeling materials. See section II of this guidance for exclusions and inclusions under the definition of material in this guidance.

requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Human- and animal-derived materials may be used directly during manufacturing of a drug substance (DS) and drug product (DP). In addition, these materials may be used in the manufacture of reagents or substrates used in manufacturing, such as cell banks, viral stocks, antibodies, and other proteins. Some common examples of human- and animal-derived materials include human or animal blood, antibodies produced in sera from animal hybridoma cells, and cytokines produced in insect cell lines.

The "materials" covered by this guidance include (1) the reagents, feeder cells[2], and excipients (and other inactive ingredients in the DP) that are in direct contact with the starting material, intermediates, and final products, (2) any materials used to manufacture reagents, feeder cells, and excipients, and (3) materials incorporated in TEMPs. The "materials" excluded from this guidance are human cells used as starting material to manufacture human cells, tissues, and cellular and tissue-based products, including TEMPs. Please refer to Gene Therapy CMC Guidance (Ref. 2) and Cell Therapy CMC Guidance (Ref. 3) for guidance on the use of cellular materials, such as cell banks used to manufacture cell therapy DPs, transduced cells that constitute gene therapy DPs, and primary allogeneic cells used as DPs.

Sponsors of IND applications for new DPs, including investigational CGT products and TEMPs, must describe the CMC information as prescribed in Title 21 of the Code of Federal Regulations (CFR) section 312.23 for the DS (21 CFR 312.23(a)(7)(iv)(*a*)) and the DP (21 CFR 312.23(a)(7)(iv)(*b*)). A regulatory submission must describe the safety and quality of materials used in manufacturing (21 CFR 312.23(a)(7)(i)). FDA may place the IND on clinical hold if the IND does not contain sufficient CMC information "to assess the risks to subjects of the proposed studies" (21 CFR 312.42(b)(1)(iv)) 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)). The use of human- and animal-derived materials at any point in the manufacturing process can affect the safety, potency, purity, and stability of the final product.

Use of human- and animal-derived materials during product manufacturing may increase risks of infectious disease transmission, and raises potential safety concerns, such as the possible introduction of adventitious agents or other impurities into CGT products and TEMPs. Thus, human- and animal-derived materials should be thoroughly characterized and described in your regulatory submission.

[2] Human- or animal-derived cells used for manufacturing of gene therapy viral vectors are not considered as feeder cells and are beyond the scope of this guidance.

Human- and animal-derived materials can also contribute to product variability by affecting the reproducibility of your manufacturing process or the quality of your final product. For example, differences among serum lots used for cell culture may lead to differences in cell growth rate or differentiation potential. Concerns regarding product variability and quality underscore the need for early studies to define critical attributes for materials and to establish acceptance criteria for specified attributes of each material.

This guidance includes recommendations when developing CGT products and TEMPs that are manufactured using human- and animal-derived materials. These considerations include donor screening and testing, adventitious agent testing and screening, risk assessment, and materials management. The guidance also includes points to consider for manufacturers of human- and animal-derived materials used in the manufacture of CGT products or TEMPs.

III. GENERAL RECOMMENDATIONS: HUMAN- AND ANIMAL-DERIVED MATERIALS

In your IND, you must provide a list of all materials used in manufacturing and a description of the quality or grade of these materials (21 CFR 312.23(a)(7)(iv)(*b*)). We recommend that you provide such list in tabular format, including, but not limited to, manufacturer, catalog number, source (e.g., human, animal, bacterial, insect), grade, and stage at which the material is used in the manufacturing process (e.g., culture media, excipient). In submissions adhering to the Common Technical Document (CTD) organizational structure, this information may be provided in sections 3.2.S.2.3 (Control of Materials) and 3.2.P.4 (Control of Excipients).

If your product is subject to FDA's CGMP regulations, you must develop and implement materials management procedures for all materials, including supplier qualification and relevant acceptance criteria for materials arriving at the manufacturing facility (21 CFR part 211, subpart E).[3] Furthermore, such materials must be held in quarantine before they have been tested or examined, whichever is appropriate, and released (21 CFR 211.82(b)). Quarantine procedures minimize the risk of introduction of adventitious agents into the facility and manufacturing process.[4] We recommend that you provide documentation in your regulatory submission that the material used for manufacturing meets standards appropriate for its intended use (e.g., specifications, Certificates of Analysis (COA), Certificates of Origin (COO), package inserts). For human- and animal-derived materials, documentation provided in the regulatory submission should include the source of the material and/or specifications for adventitious agent testing performed by the supplier, as appropriate. Please note that manufacturers of the CGT or TEMP product may need to perform additional testing of the material before acceptance by the

[3] An investigational drug for use in a phase 1 study is subject to the statutory requirements set forth in section 501(a)(2)(B) of the Federal Food, Drug & Cosmetic Act (FD&C Act) (21 U.S.C. 351(a)(2)(B)). The production of such a drug is generally exempt from compliance with the CGMP regulations in 21 CFR parts 210 and 211. See 21 CFR 210.2(c). However, the general principle of material controls is also important for investigational drugs for use in a phase 1 study.

[4] For this reason, the practice of quarantining is advisable when manufacturing products for use in a phase 1 investigation that are not subject to the CGMP regulation in 21 CFR 211.82.

manufacturing facility if the testing performed by the supplier is not sufficient to assure the safety of the DS or DP in the context of the manufacturing process.

For all materials, we recommend that you use materials of the highest quality available, which may include articles that are FDA-licensed, -approved or -cleared and used as materials, if appropriate. Alternatively, you may wish to consider using materials that are free of human- or animal-derived proteins (e.g., tissue culture media free of human or animal-derived materials,[5] recombinant proteins), because they may have fewer safety risks and may be less variable in their composition, thus avoiding donor-to-donor variability, and avoiding the variability in how such proteins affect cellular or tissue growth and properties.

A. Adventitious Agents

Human- and animal-derived materials increase the risk of introducing adventitious agents, including viruses, parasites, bacteria, mycoplasma and agent(s) responsible for transmissible spongiform encephalopathies (TSEs). If the manufacturing process of the material includes steps that you rely upon to remove or inactivate potential infectious contaminants from these materials, the regulatory submission should describe how the manufacturing method for the material has been demonstrated to remove adventitious agents. For example, you or the manufacturer of the material should qualify the processing methods and any sterilization techniques used in material manufacture for their ability to inactivate and remove infectious contaminants. If removal or inactivation of the potential infectious contaminant cannot be demonstrated, such as agent(s) responsible for TSEs, careful source material selection may be a risk mitigation strategy.

The introduction into a manufacturing facility of a material that is contaminated with an adventitious agent carries the risk of contaminating other products or infecting personnel with the adventitious agent. For example, a mycoplasma contamination introduced via a material can be spread to equipment and personnel. We recommend that you develop procedures to ensure that contaminated materials do not compromise the quality and purity of the product. In cases where adventitious agent testing or examination of materials is pending at the time of receipt, quarantining the material until completion of the testing must be part of an overall current good manufacturing practice (CGMP)-compliant strategy under our CGMP regulations (21 CFR 211.82).[6]

B. Risk Management Process

As described in FDA's "Guidance for Industry: Q9(R1) Quality Risk Management," dated June 2006 (Ref. 4), risk assessment consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards. A risk management process consists of a systematic process encompassing risk assessment,

[5] Please note that "serum-free" medium and supplements may still contain human or animal components (see section IV.C.4 of this guidance).

[6] As stated above, the practice of quarantining is advisable when manufacturing products for use in a phase 1 investigation that are not subject to the CGMP regulation in 21 CFR 211.82.

control, review, and communication. You should assess the potential risk for introduction of adventitious agents by human- and animal-derived materials. Process qualification or viral clearance validation studies can help to assess risk, and the manufacturing process can be designed to mitigate risks, where appropriate. As mentioned above, contaminated materials may present unacceptable risks to the manufacturing environment, and these risks should be evaluated in your risk assessment.

We recommend that you provide risk assessments of human- and animal-derived materials in CTD section 3.2.A.2 of your regulatory submission. We recommend that the risk assessments include consideration of the source of the material (species and geographical origin). Moreover, you should describe how your material acceptance specifications mitigate risks. Finally, for all materials, you should list the manufacturing steps where the material will be used. In CTD format, you should list all the materials and the steps where they are used in sections 3.2.S.2.3 (Control of Materials) and sections 2.3.P.4 (Control of Excipients).

You should consider the potential impact of the change in suppliers of such materials. A change in suppliers may have a profound effect on material safety and quality, given that different suppliers may use a different starting material, pool sizes, and manufacturing approaches. Such an effect on the material could significantly alter the safety or quality of the CGT product or TEMPs being manufactured.

C. Material Acceptance Testing

CGMP regulations require identity testing of materials, and specific tests should be used if they are available (21 CFR 211.84(d)(1)). Although the production of an investigational drug for use in a phase 1 study is exempt from compliance with the regulations in 21 CFR part 211 (21 CFR 210.2(c)), manufacturers must follow statutory CGMP required under section 501(a)(2)(B) of the FD&C Act[7], and you should consider implementing identity testing, even during phase 1 clinical investigations, in order to minimize any unintended compromise to product safety or quality. For example, if there is a similar material being used in the same facility, such as similar types of sera or media supplements, it is important to verify material identity. For phase 1 investigations, you should establish written procedures describing the handling, review, acceptance, and control of materials used in the manufacture (Ref. 5).

Materials must be tested for conformance with all appropriate written specifications for purity, strength, and quality; or alternatively you may rely on a report of analysis from the supplier, provided that the manufacturer conducts at least one specific identify test and establishes the reliability of the supplier's analyses (21 CFR 211.84(d)(2)). Your risk analysis should determine whether it is adequate to rely on testing performed by the supplier and reported on a COA, or whether you should also perform additional tests prior to acceptance of a material. For example, if not reflected in the COA, it may be

[7] See Reference 5.

important to perform tests for potentially harmful impurities in the material, or functional testing to ensure that the material will perform as intended and with adequate reproducibility in your manufacturing process.

Materials of human or animal origin may show donor-dependent variation in purity, strength, and quality profiles. When a material is a biologically complex mixture that may vary among lots, it is important to establish acceptance criteria for the attributes that will affect the performance of the material in your product manufacturing process. For example, materials derived from blood are frequently pooled during material manufacturing. Pooling is generally thought to improve lot-to-lot consistency of the material, but it may still be necessary for either you or the supplier to test certain attributes of the material to ensure that new lots will perform adequately in your product manufacturing process. The level of pooling may vary considerably by supplier, or even among lots from the same supplier.

Material consistency can be evaluated by assessing material performance because changes in performance may indicate that the material is not consistent. To help ensure material consistency, we therefore recommend that you evaluate whether it is necessary to test material performance when accepting a new lot (e.g., including an assay to evaluate whether the new lot of material performs adequately and as intended, including a comparison to previously used lot(s), if applicable). For example, in some cases you may determine that it is necessary to test the ability of each new lot of human serum to support growth of the cell lines used during manufacturing of your product. For some materials you may decide, after determining that different lots from the same supplier produce similar results, that you have sufficient confidence in the supplier's testing that no additional testing is needed.

Testing for relevant communicable disease agents or diseases should be performed using donor screening tests that are licensed, approved, or cleared by FDA specifically for donor screening, not only for in vitro diagnostic testing.[8] Because of the difference in the intended population and how the results are used, donor screening tests are approved based on different standards compared to those intended for diagnostic purposes. You should also document the size of the pool of donor material and verify that any tests for human infectious agents that were performed on the pooled material are approved by FDA for testing pools of that size (FDA-approved tests are approved for specific matrices and specific pool sizes, as stated on the specific tests' Instructions for Use). Human- and animal-derived materials should generally also be tested for microbiological contamination.

[8] Please note that for human cells, tissues, and cellular and tissue-based products (HCT/P's) subject to 21 CFR part 1271, it is required that testing be performed using appropriate FDA-licensed, approved, or cleared donor screening tests, in accordance with the manufacturer's instructions, to adequately and appropriately reduce the risk of transmission of relevant communicable disease agents or diseases. 21 CFR 1271.80(a). However, until such time as appropriate FDA-licensed, approved, or cleared donor screening tests for *Chlamydia trachomatis* and for *Neisseria gonorrhea* are available, manufactures must use FDA-licensed, approved, or cleared tests labeled for the detection of those organisms in an asymptomatic, low-prevalence population. *Id.*

IV. MATERIALS DERIVED FROM HUMAN BLOOD AND BLOOD COMPONENTS

Human-derived materials are frequently obtained from blood and blood components,[9] including Source Plasma. Source Plasma is the fluid portion of human blood collected by plasmapheresis and intended as a source material for further manufacturing use. The definition excludes single-donor plasma products intended for intravenous use (21 CFR 640.60). Some materials used in manufacturing CGT products and TEMPs can be derived from multiple types of donated source material. For example, human AB serum can be manufactured from whole blood, single-donor plasma, or Source Plasma. The testing requirements for Source Plasma are different than those for whole blood and plasma. For example, Source Plasma, which is intended solely for further manufacturing use, is not required to be tested for human T-lymphotropic virus (HTLV), West Nile virus (WNV), and Chagas disease (21 CFR 610.40 (a)(2)(ii)) and the requirements for testing Source Plasma donations for syphilis differ from the requirements for testing donations of other blood components for syphilis (see 21 CFR 610.40 (a)(2)(i) and 21 CFR 640.65(b)(2)) (see section IV.C.2 of this guidance). Thus, your regulatory submission should document the type of donated source material (e.g., blood, plasma, platelets, Source Plasma, etc.) used to manufacture the human-derived material.

A. Collection and Testing of Donated Source Material

The collection, processing, compatibility testing, storage and distribution of human blood and blood components must be performed in accordance with applicable requirements for current good manufacturing practices (21 CFR part 606) and must be collected in accordance with applicable requirements for donor eligibility and donation testing requirements in 21 CFR part 630, subpart B, 21 CFR part 640, and 21 CFR 610.40. We recommend that you source your blood and blood components from blood establishments that are FDA-registered.[10]

In your regulatory submission, please include a statement that collection of the blood or blood component is performed by a registered blood establishment to ensure that blood and blood components are collected, processed, and tested per appropriate regulations cited above. In addition, we recommend that you document the type of donated source material and the tests performed on this material (for blood or blood components). If testing was performed on pooled donated source material (e.g., a plasma pool), we recommend that you document that the pool size for each test does not exceed the pool size for which the test has been licensed, approved, or cleared by the FDA. Please be aware that the testing requirements and recommendations outlined in this guidance may differ depending on the type of blood component, as discussed in section IV of this guidance.

[9] See definition of blood component at 21 CFR 606.3(c).

[10] We make this recommendation throughout the draft guidance. FDA-registered establishments are in FDA's database for scheduling inspections and are subject to periodic inspection to ensure compliance with applicable regulations.

B. Reducing Risks of TSE in Human-Derived Materials

In general, TSE may be transmitted between humans, and thus, human-derived materials pose a risk of TSE transmission. Creutzfeldt-Jakob Disease (CJD) and variant Creutzfeldt-Jakob Disease (vCJD) are relevant transfusion-transmitted infections (RTTI) diseases under 21 CFR 603.3(h) and blood establishments must assess a donor's medical history to identify risk factors closely associated with an RTTI. The guidance titled, "Recommendations to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease and Variant Creutzfeldt-Jakob Disease by Blood and Blood Components," dated May 2022 (CJD guidance) (Ref. 6), outlines the possible risks associated with the transmission of CJD (a type of TSE) and vCJD by blood and blood components and provides donor deferral recommendations. We recommend that human blood-derived materials are derived from donations collected at blood establishments that follow the recommendations in the CJD guidance.

C. Special Considerations for Commonly Used Human-Derived Materials

1. Human Platelet Lysate (HPL)

HPL is the soluble fraction isolated from disrupted platelets, and HPL may be used by manufacturers as a growth medium supplement to substitute for serum. The types of donated source material for HPL include expired licensed platelets, whole blood, platelet-rich plasma, and apheresis platelets or platelets collected by apheresis. HPL is obtained through repeated freeze-thawing cycles, sonication, or by applying platelet activators such as thrombin or calcium chloride. If using HPL, we recommend that you provide the following information:

- If platelets are used as a starting material to manufacture HPL, you should document whether expired or non-expired units of platelets were used because the stability of platelet-associated growth factors may be affected by length of storage. You should describe the acceptance criteria for expired platelets (e.g., length of storage, the minimum levels of a certain growth factor, etc.).
- You should provide documentation that the donated source material is collected at an FDA-registered blood establishment in accordance with 21 CFR part 640, subpart C requirements and ensure that the platelets are collected, processed, and tested per appropriate regulations cited above.
- You should include information about how the donated source material is stored.
- To address possible concerns about cross-contamination, you should describe the procedures used to prepare HPL, provide information on any materials or equipment involved in its production, and indicate the facility used.

2. Human Serum

Human serum, such as AB serum, is generally obtained from plasma, Source Plasma, or whole blood. In your IND, you should describe the whole blood or plasma testing, collection, and processing procedure. We recommend that you document that collection, testing, and processing are performed in compliance with 21 CFR part 606 and 21 CFR part 640, subparts A, D, or G at an FDA-registered blood establishment.

Manufacturers of Source Plasma are not required to test donations for certain RTTI, including HTLV, WNV, Chagas disease, or babesiosis (21 CFR 610.40).[11] Source Plasma donations are tested for syphilis in accordance with 21 CFR 640.65(b)). Source Plasma has unique testing requirements because it is intended to be used for further manufacturing of plasma-derived biologic products that are manufactured using validated viral inactivation/removal procedures such as column chromatography, detergent treatment, or extensive heat inactivation. Human AB serum manufacturing processes do not typically include such manufacturing steps. Consequently, we do not consider Source Plasma to be an appropriate starting material for human AB serum manufacture, unless you can provide documentation that the Source Plasma was tested using FDA-licensed, approved, or cleared donor screening tests for HTLV, Chagas, WNV, babesiosis, and syphilis to align with the requirements for other blood components as required in 21 CFR 610.40.

You should document the entire human AB serum manufacturing process, starting with any processing steps performed on the donated source material, defibrination steps (if applicable), and the conditions of heat inactivation (time and temperature) and irradiation (type of irradiation and irradiation dose in kGy), if applicable. If bovine thrombin is used during manufacture, documentation supporting its safety should be submitted. Safety may be supported by data demonstrating freedom from bovine adventitious agents in the bovine thrombin.

3. Human Serum Albumin (HSA)

In general, HSA used as an excipient in a CGT or TEMP product should be licensed in the United States (U.S.), since the HSA will be directly administered to the patient and the use of licensed HSA helps ensure safety and quality. For HSA used in manufacturing of CGT products and TEMPs not as an excipient, we recommend that you use U.S.-licensed or U.S. Pharmacopeia (USP)-grade albumin to also help ensure safety and quality. If you choose to use a version of human blood-derived HSA that is not licensed in the U.S. in the manufacture of CGT products and TEMPs, we recommend that you provide a justification for such use.

[11] If the human AB serum is derived from plasma or whole blood, it is important to note that testing for Zika virus is no longer required for human blood and blood components, including plasma and serum (Ref. 7).

You should provide information on the HSA used at any point in your manufacturing process. If using a licensed albumin, you should indicate which licensed product is being used and provide a copy of the package insert.

4. Human-Derived Proteins in Culture Media

Human blood-derived proteins can be added to culture media. For example, transferrin is a blood protein that is used as a media additive to minimize oxidative stress by chelating iron. It is often added as a supplement to "serum-free," "serum-reduced," "xeno-free" or other supplemented cell culture media. For example, although there are recombinant forms of transferrin, commercial media formulations often contain human plasma-derived transferrin. The presence of a human-derived protein in cell culture media, such as transferrin or HSA, may not be immediately apparent on the COA supplied for the medium. Therefore, you should document in the submissions to FDA the presence of human-derived proteins in all media used to manufacture CGT products and TEMPs. Moreover, you should include information to document conformance to donor testing requirements specified in 21 CFR 610.40 and that the human-derived material has been manufactured using procedures that have been validated to clear or inactivate human adventitious agents. Manufacturers of culture media used in manufacture of CGT or TEMP products who wish to provide confidential information about their media to FDA should submit a Type II drug master file (DMF) to the Center for Biologics Evaluation and Research (CBER). If a MF is available for a material, a letter of authorization that authorizes the cross-reference of information in the MF and that is signed by the person who submitted the cross-referenced information should be included in an IND submission (21 CFR 312.23(b)).

V. HUMAN-DERIVED FEEDER AND BYSTANDER CELLS AND CELL-DERIVED PARTICLES

Human-derived feeder and bystander cells and cell-derived particles (e.g., extracellular vesicles, exosomes, secreted proteins) may be used to propagate human cells during manufacturing of CGT products and TEMPs. Some examples include immortalized feeder cells, allogeneic cells irradiated at high dose to yield cell particles, and cells that have been genetically modified to express certain stimulatory proteins. Ascertaining complete absence of residual cells from the final product is technically challenging, and the feeder or bystander cells and cell-derived particles may thus be present in the DS and DP as impurities. Moreover, feeder or bystander cells and cell-derived particles are frequently used in culture with CGT products or TEMPs for prolonged periods of time, which may increase the risk of transmission of adventitious agents from the feeder cells to cells in the final product. For these reasons, we recommend that feeder and bystander cells and cell particles derived from human cells should be derived from donors who meet the eligibility criteria in 21 CFR part 1271, subpart C. We also recommend that feeder and bystander cell banks are tested for sterility, mycoplasma, relevant human adventitious

agents, including, but not limited to, in vivo adventitious agent testing (master cell bank), in vitro adventitious agent testing (master cell bank and working cell bank), viral particles by transmission electron microscopy, human pathogens by polymerase chain reaction, and retroviruses, if the cells come into contact with non-human cells and/or reagents. The extent of testing may depend on the banking and expansion strategy, and, if feeder and bystander cell bank testing is limited, it may be necessary for the cellular product manufacturer to demonstrate that the drug substance or drug product is free of potential adventitious agents. Testing for species-specific viruses may also be required if the banks are produced using animal-derived materials. For relevant concepts on the methods, please refer to "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. 8).

VI. MATERIALS DERIVED FROM ANIMALS

For all animal-derived materials, we recommend that you conduct testing consistent with the testing described in 9 CFR 113.47 and 9 CFR 113.53.

A. Animal-Derived Feeder Cells

For feeder cells and feeder cell particles from animals (e.g., murine feeder cells), we recommend that cell banks are tested for relevant animal adventitious agents, including, but not limited to, in vivo adventitious agent testing (master cell bank), in vitro adventitious agent testing (master cell bank and working cell bank), and retroviruses. If a feeder cell line of animal origin is used to propagate human cells (i.e., if human and non-human cells are co-cultured), we would consider the final product to be a xenotransplantation product.[12]

B. Bovine- and Ovine-Derived Materials

To assure the safety of bovine-derived materials, we recommend following the procedures described in 9 CFR 113.47 and 9 CFR 113.53, and the recommendations in Cell Therapy CMC Guidance, and Gene Therapy CMC Guidance (Refs. 2 and 3). In addition, please refer to Cell Therapy CMC Guidance and Gene Therapy CMC Guidance (Refs. 2 and 3) for information about documentation of bovine spongiform-related risks. Even if bovine-derived materials are not used directly in the manufacture of CGT products or TEMPs, you should document whether bovine material is used during the manufacturing of any material used to manufacture CGT products or TEMPs. For example, some enzymes are manufactured from bacteria that are grown in media that contain bovine-derived materials, meaning that if the enzyme is used in manufacture of the product, the above-cited safety considerations should be addressed. If your manufacturing process uses a recombinant protein derived from bacterial fermentation, you should identify and document any bovine-derived materials used for bacterial

[12] For information on xenotransplantation products, please refer to Refs. 9 and 10.

fermentation and protein purification. Bovine and ovine materials, such as albumin, are sometimes added as carriers in the formulation of small quantities of protein reagents. In cases where obtaining the documentation may be difficult, we recommend that carrier-free materials be used in manufacturing. For all bovine-derived materials, including those with indirect contact, you should provide documentation reflecting freedom from adventitious agents and bovine spongiform encephalopathy (BSE) (e.g., documentation that the herds are born, raised, and slaughtered in a country with negligible BSE risk).

C. Porcine-Derived Materials

The Cell Therapy CMC Guidance and Gene Therapy CMC Guidance outline the concerns associated with porcine materials (Refs. 2 and 3). Trypsin is a commonly used material that is derived from pigs. We recommend that you use a trypsin alternative that is free of porcine-derived materials, if it is appropriate for your specific application. For safety testing of porcine materials, we recommend testing consistent with the testing for ingredients of animal origin used for production of biologics described in 9 CFR 113.53 and consistent with the test methods outlined in 9 CFR 113.47. Documentation should also demonstrate that the porcine-derived materials are tested for porcine circovirus (PCV) 1 and 2 and porcine parvovirus.

D. Insect-Derived Materials

Cytokines and other proteins may be manufactured using insect cell lines. Insect-derived materials may introduce rhabdovirus (Ref. 11) and spiroplasma (Ref. 12). Thus, materials made in insect cell lines should be tested for rhabdovirus, mycoplasma, and spiroplasma. You should submit additional information regarding any additional specific adventitious viral agent testing that was performed on the material and/or cell line and describe any viral clearance/reduction procedures that were performed during purification of the material.

E. Materials From Other Animals

You should closely examine the formulations of media and enzymes, because the use of animal-derived reagents may not be readily apparent on the COA. For instance, chicken egg-derived lecithin is a media additive, and some enzymes may be derived from crustaceans. Moreover, non-mammalian animal-derived materials may be used in fermentation of bacteria used to produce enzymes. If specific pathogen-free animals are available, we recommend that materials be sourced from specific pathogen-free animals. Your regulatory submission should contain information regarding any testing for relevant animal pathogens, including the acceptance criteria for any animal tissues that are used in the manufacture of the material. You should also submit the results of testing and release criteria for animal tissues used in TEMPs (e.g., parts of DS or DP of the TEMP derived from animal source such as porcine-derived extracellular matrix). You should perform a risk assessment and document any viral inactivation steps present in the manufacture of the animal-derived material.

VII. RECOMBINANT MATERIALS

Recombinant human or animal proteins, such as growth factors and antibodies, particularly growth factors marketed for research purposes, may contain impurities or contaminants from the expression system. This may also include adventitious agents. Monoclonal antibodies may be used as reagents in drug manufacturing, and we recommend that you refer to "Guidance for Industry: Monoclonal Antibodies Used as Reagents in Drug Manufacturing," dated March 2001 (Ref. 13) for considerations to ensure that monoclonal antibodies are free of adventitious agents or process-related impurities. In addition, some growth factors may be purified by affinity chromatography using monoclonal antibodies that have not been tested for adventitious agents. It is your responsibility to obtain appropriate information regarding any purification of all recombinant materials used in the manufacture of your CGT products or TEMPs.

VIII. TISSUE-ENGINEERED MEDICAL PRODUCTS

TEMPs commonly incorporate cells and scaffolds. Manufacturing of TEMPs may include animal- and human-derived materials, such as media, media supplements, and scaffolds. Unlike other types of materials used in product manufacturing, scaffolds may be an integral part of the final formulated TEMP that contributes to the intended therapeutic effect. The general concepts outlined in this guidance for animal- and human-derived materials apply to TEMPs, including those that may become a part of a DS or DP. In cases where TEMPs include a device constituent derived from animal sources (e.g., an animal-derived scaffold used as a part of a cell-scaffold construct may be classified as a device constituent part in certain TEMPs), we recommend that you follow the recommendations in the FDA guidance "Medical Devices Containing Materials Derived from Animal Sources (Except for In Vitro Diagnostic Devices); Guidance for Industry and Food and Drug Administration Staff" dated March 2019 (Ref. 14) which contains additional guidance regarding animal-derived materials used in devices.

The use of materials derived from animal tissues and organs in TEMPs poses the risk of transmission of animal adventitious agents. For decellularized tissue matrix, you should provide evidence of the absence of cellular material, both viable and non-viable, document the methods of decellularization and terminal sterilization (if applicable), and document the sterilization assurance level. If you are relying on decellularization and sterilization methods for viral inactivation, you should submit data demonstrating the viral inactivation properties associated with the manufacturing and/or sterilization processes. The results of your viral inactivation studies should include the sum of the $\log_{10}$ reduction in virus from selected processing steps and sterilization process(es) (i.e., the overall virus reduction factor).

Extracellular matrix scaffolds and proteins abundant in the extracellular matrix (e.g., collagen) derived from animals may also be used in TEMPs. As for all animal-derived materials, it is important to document the sourcing and testing of animal tissues and to document capabilities of the manufacturing and sterilization processes to eliminate animal pathogens.

IX. COMMUNICATION WITH THE FDA REGARDING THE USE OF HUMAN- AND ANIMAL-DERIVED MATERIALS

We recommend communication with the Office of Therapeutic Products (OTP) in CBER early in product development, before submission of an IND, via pre-IND (Ref. 15) or INitial Targeted Engagement for Regulatory Advice on CBER producTs (INTERACT) meeting request.[13] In your pre-IND or INTERACT meeting request, we recommend that you include specific questions about human- and animal-derived material safety and quality and provide sufficient background information to support their safety and quality, as outlined above, in this section of the guidance. Changes to materials for products under an IND or a biologics license application (BLA) should be reported in an IND amendment or BLA supplement, respectively.

[13] For additional information about INTERACT meetings, please see https://www.fda.gov/vaccines-blood-biologics/industry-biologics/interact-meetings.

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