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IPRP Reflection Paper

General Considerations for Raw Materials Used in the Manufacture of Human Cell and Gene Therapy Products

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Disclaimer

This document reflects the views of subject matter experts participating in the IPRP Cell Therapy Working Group (CTWG) and Gene Therapy Working Group (GTWG) and should not be construed to represent the official views of any given regulatory authority participating in the IPRP.

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1. Position Statement

The International Pharmaceutical Regulators Programme (IPRP) Cell Therapy Working Group (CTWG) and Gene Therapy Working Group (GTWG) have prepared this reflection paper to provide their perspectives on quality of raw materials used in the manufacture of investigational and licensed human cell or gene therapy (CGT) products. For the purposes of this reflection paper, raw material is a general term used to denote reagents, solvents, and excipients intended for use in the production of cell or gene therapy products.

The points to consider outlined in this paper are not applicable to active substances and starting materials from which the active substance is manufactured or extracted (e.g., viral vectors, transposons, genome editing components, plasmids used for production of viral vectors, and cellular source materials). The scope of this document excludes donor eligibility, as donor eligibility is regulated differently in various regions.

Raw materials used in the manufacture of human CGT products can impact product quality, and, consequently, the product safety and effectiveness. Therefore, the potential risk introduced by raw materials to CGT product quality should be evaluated and managed through adequate processing and testing of the raw materials and appropriate controls and testing in line with Good Manufacturing Practice (GMP) in the manufacturing of the CGT product.

2. Background

This reflection paper provides considerations of risks introduced by raw materials used in the manufacture of CGT products as well as recommendations for risk management. CGT products are complex and generally sensitive to manufacturing conditions and variations in quality of raw materials. Moreover, the impact of raw materials on the quality, safety, and efficacy of CGT product quality is often difficult to predict. CGT products are often subjected to risk of contamination by raw materials of biological origin used in their manufacture. Additionally, stability and function of raw materials may impact CGT product quality. Therefore, the potential risks associated with raw materials should be thoroughly assessed by the manufacturer of the CGT product and mitigated through selection and control of raw materials, as well as control of the CGT product.

3. Risk Assessment for Raw Materials

Raw materials may impact CGT product quality, safety, and efficacy. Moreover, they may introduce impurities, which can have an unintended impact. The risk of raw materials to product quality should be assessed and managed by the quality management system (QMS). CGT manufacturing processes should be optimized to minimize or eliminate the use of raw materials of biological origin. A risk assessment should be conducted by CGT manufacturer regarding the selection of the raw materials used, taking into account parameters such as the source, grade, traceability, documentation provided, available vendors, and possible contamination sources. The risk assessment should also consider the ability of the manufacturing process to control or remove the raw material from the final drug product. In doing a systematic risk management of raw material, the manufacturer can refer to ICH Q9 guidance titled “Quality Risk Management.”

Any risk factor must be evaluated in relation to the clinical benefit/risk of the CGT product. When evaluating the risk posed by the raw material to the final medicinal product, the exposure of a patient to

residual amounts of raw material with potential harmful effects (e.g., adverse immune reactions) should be considered in relation to the clinical benefit/risk of the CGT product.

3.1 Suitable Quality Management System

The manufacturer of the CGT product should establish a QMS that includes a raw materials qualification program. The raw materials qualification program should ensure the quality of raw materials entering the CGT product manufacturing facility and used in the CGT manufacturing process through:

- Risk assessment as described in Section 3.2 *Impact of raw materials on quality of CGT products.*
- Suppliers'[1] approval, monitoring and/or auditing, whenever applicable, and quality agreements with the suppliers of raw materials, including change control. Moreover, a change in supplier or manufacturer of a raw material may impact its quality. Therefore, manufacturers of CGT products should secure a reliable supply chain to assure consistent performance of raw materials.
- Review of Certificates of Analysis (COAs) and other supporting documents to verify proper documentation and conformance of release test results, and/or performance of any additional required in-house tests (See Section 5.1 *Pre-defined raw material quality specifications*).
- Appropriate procedures for quarantine/segregation and storage of raw materials.
- Stability assurance and documentation of expiry period.

3.2 Impact of Raw Materials on Quality of CGT Products

Risk assessment for raw materials should consider their source (non-biological, biological, recombinant, human, or animal-derived). For animal-derived raw materials, species and geographical origin are also of concern. For human-derived raw materials, donor eligibility criteria should be included in the risk assessment, whenever applicable. Information on the raw materials' manufacturing process, the quantity of raw materials introduced into the CGT manufacturing process, their testing, and knowledge of the acceptable permissible single exposure levels in humans should be taken into consideration.

The risk of adventitious agents, such as viruses, bacteria, mycoplasma, prions, or yeasts that may be introduced into CGT products via raw materials should be assessed and reduced through appropriate selection of the raw material considering its source (e.g., human, animal, bacterial, insect, non-biological) and manufacturing process (e.g., steps to reduce or eliminate microbial and viral contamination, if applicable), and appropriate testing of the raw material (e.g., microbial controls, adventitious agent testing). Additionally, the risk of contamination should be controlled through the manufacturing process and control of the overall CGT product and testing on intermediates, drug substance (DS), or drug product (DP), as applicable.

A risk assessment should evaluate the risk of toxicities, such as toxicities introduced by cytokines, antibodies, synthetic components, and other byproducts/impurities generated during the manufacturing process. The CGT manufacturer should address any risk of toxicity by limiting the quantity of the raw material with toxicity introduced into the CGT manufacturing process and controlling their residuals levels in the DP. The permissible single exposure levels of impurities with potential for toxicities in human recipient should be determined through experimental setting (e.g., animal studies), literature, or another

[1] In this document, "supplier" is the business that provides/sells the raw material to the CGT manufacturer. The supplier may or may not be the manufacturer of the raw material.

scientific knowledge, such as comparison to general thresholds of toxicological concern, before it is decided if additional information/experiments are necessary. While in some cases, the test results obtained from the manufacturer of the raw material (e.g., COA) are sufficient, in other cases, the risk assessment may determine that further testing of the raw material is needed to evaluate the raw material's risk before introducing it into the CGT manufacturing process.

The overall control strategy addressing the risk associated with the use of raw materials should be described by the CGT manufacturer. The CGT product manufacturing steps where the raw materials are introduced should be considered. Often, introduction of raw materials upstream in the CGT manufacturing process may decrease the risk associated with raw materials through washing steps and dilution and/or additional intermediate or DS testing (e.g., adventitious agent testing). Depending on the risk, release testing for residual raw materials in the DP may be necessary in some cases. In other cases, qualification studies demonstrating removal of impurities from the CGT product may be sufficient. A risk assessment on the impact of impurities may be sufficient in early phase of development.

The CGT product manufacturer should assess all changes to raw materials and suppliers. If the change has a potential to impact product quality, comparability of the pre- and post-change CGT product may need to be evaluated. For example, different suppliers may use different manufacturing approaches (e.g., recombinant cytokine produced by different manufacturers) or different source materials (e.g., human AB serum that is "off-the-clot" vs. plasma-derived) for manufacture of the same raw material. These changes can introduce variability into CGT manufacture and resulting product or significantly alter the safety and/or quality thereof.

3.3 Origin and Traceability

Raw materials should be accompanied by appropriate documentation, such as Certificate of Origin (COO), enabling traceability and identification of the origin of raw materials and/or components used in their manufacture. Traceability enables the identification and tracking of the raw materials throughout the CGT manufacturing process and is typically achieved by the assignment of identification number (e.g., lot number), recording, and labeling. For example, in case of contaminated CGT product, documentation may be critical in investigating and tracing raw material lot(s) with potential relevance.

For certain geographical regions, there is an increased risk of infectious agents, and therefore, the origin and traceability of raw materials and/or of components used in the manufacture of the raw materials should be considered. For example, raw materials of human and animal origin may have an increased risk of contamination with adventitious agents, including viruses and Transmissible Spongiform Encephalopathy (TSE)/Bovine Spongiform Encephalopathy (BSE). Some regulators may not accept human or animal-derived raw materials derived from specific tissues or sourced from specific geographical areas. The specifics of which origin is acceptable or not and which test is required to mitigate the risk introduced by the origin is deferred to each competent regulatory authority. If raw material of human or animal origin is used, the CGT product manufacturer should select raw materials for which information is available on the sources of the raw materials. This can be implemented as a part of a supplier qualification and may include an agreement with the supplier to only provide raw material manufactured from source material from specific regions.

4. Production of Raw Materials

4.1 Suitable Process Controls

For non-compendial raw materials and materials of biological origin, sufficient knowledge of their manufacturing process and control should be available to allow evaluation of any potential risk and to establish additional controls, as needed. Description of raw materials production and documentation of critical process controls enables the CGT product manufacturers to evaluate any potential risks and to establish additional controls, as needed. For example, the type of filter used to remove particles or adventitious agent should be documented to allow further assessment of the potential for remaining contaminants of certain size in the raw material.

4.2 Microbial Safety

Most CGT products do not go through terminal sterilization. Therefore, sterility of raw materials used in the manufacture of the CGT product is critical. While certain types of raw materials can be terminally sterilized using high heat or irradiation, other raw materials (e.g., materials of biological origin) cannot. Raw materials that cannot be terminally sterilized should be manufactured using aseptic processing and when feasible, sterile filtration step can be implemented to eliminate microbial contaminants without compromising the quality of raw materials. Sterility testing should be performed on raw materials used in manufacture of CGT products, and the results should be documented, if this information is not available from the supplier. If the raw material is not sterile, the level of microbial contamination must be known. Mycoplasma testing of raw materials might be needed for raw materials manufactured using human or animal cells, if this information is not available from the supplier.

Traditional viral inactivation/removal procedures (e.g., heat, detergent, low pH, or filtration) are generally not suitable for CGT products. Therefore, when possible, raw materials that have undergone viral inactivation/removal steps using validated procedures should be preferred if raw material of biological origin is used. If such steps are not feasible, the raw materials should be thoroughly tested for the presence of relevant viruses and their use should be justified.

4.3 Use of Additives

Additives (specific ingredients of raw materials), such as stabilizers, are frequently added to raw materials to improve their stability, provide nutrients, support, or inhibit cell growth. In cases where stabilizers of biological origin are used in the production of the raw material, their presence should be justified, and the risks associated with such additives assessed. For instance, animal-derived proteins, such as transferrin, carry the risk of transmission of adventitious agents, including prions. Transferrin is a blood protein that is used as a media additive to minimize oxidative stress by chelating iron. The presence of transferrin may not be immediately apparent on the COA of media and/or other raw materials issued for a medium marketed as “serum-free”, “serum-reduced,” or “xeno-free.” The COO of media or other raw materials that may contain additives of biological origin should be thoroughly examined for viral/TSE safety of animal- and human-derived components. CGT manufacturers should work with suppliers of raw materials to provide documentation on adventitious agent safety, with the level of documentation varying on the type of material of any animal- or human-derived additives/ingredients contained in the raw

material. Introduced changes in additives may require requalification of the raw material and/or the supplier.

5. General Recommendations

5.1 Pre-defined Raw Material Quality Specifications

Raw materials used in the manufacturing process of CGT products should be controlled, in part, through testing against specifications that ensure their suitability for the intended use and acceptable lot-to-lot variability. In-house manufactured raw materials are also in the scope of this sub-chapter.

Extent of testing may depend on the criticality and complexity of raw materials (e.g., biological, recombinant, synthetic). Testing of raw materials can be performed by the manufacturer of the raw materials, the CGT manufacturer or a contract laboratory, and the results are typically provided on a COA. A raw material may be accepted using verification of raw material quality attributes based on a supplier's COA (e.g., for compendial or non-biological raw materials) provided that the CGT manufacturer has a system in place to qualify suppliers. Periodic confirmatory in-house testing may be considered. In some instances, testing of the raw material (e.g., identity and, if applicable, functional attributes) is recommended to be performed by the CGT manufacturer for non-compendial and biological materials, as applicable. Acceptance criteria for quality attributes should be appropriately justified. Where necessary, the following quality attributes may be considered when evaluating raw materials:

- The suitability of raw materials for the intended use should be ensured, including –where appropriate– by means of testing, including identity testing, as applicable. Identity tests can be used to verify the identity of each batch of raw material and be suitable for differentiating between similar raw materials used in the manufacturing facility.
- Functional attributes (biological or otherwise) should be controlled to achieve their intended use, if applicable. For example, biological materials, such as cytokines and sera, may have significant batch-to-batch variability that may affect the reproducibility of the manufacturing process or the quality of the DP. As such, functional testing of these raw materials should be implemented as part of raw material qualification.
- Purity and safety attributes such as sterility, endotoxin, and mycoplasma should be considered based on risk assessment. Undesired impurities, such as those with known carcinogenicity or potential for immunogenicity, should also be evaluated.

5.2 Tests/Assays Used for Raw Material Qualification

In some instances, the supplier's COA may not be adequate for verification of non-compendial raw materials and raw materials. In such cases, raw material qualification and should be supplemented with a suitable panel of tests to be performed by the CGT manufacturer or a contract laboratory. With regard to the test methods, the following should be considered, as applicable:

- Any analytical methods selected for testing of quality attributes should be appropriate for their intended use.
- Compendial methods should be used when possible and be appropriately verified.
- Where compendial methods are not available, in-house analytical methods should be developed as early as feasible based on specific requirements of the process and product.
- Whenever applicable, an established reference standard/batch or appropriately qualified reference material should be included in the assay.

5.3 Quality of Raw Materials Used in Manufacture of CGT Products

Multiple quality grade categories exist for raw materials: (1) licensed/authorized materials for human use (i.e., approved by a relevant regulatory agency), (2) compendial materials, (3) raw materials subject to in-house specification (i.e., a combination of supplier and in-house testing), and (4) raw materials of research grade. Also, a raw material may be manufactured at a facility designed, built and claimed to be in compliance with GMP. The use of "GMP grade" to address a raw material quality does not reflect the quality of the raw material itself because GMP standards are not required for the manufacture and quality control of raw materials. The amount of supporting information provided for a raw material may depend on the raw material's risks and grade. The following general concepts should be considered for quality of raw materials used in CGT products:

- As far as possible, licensed or compendial materials should be used in manufacturing of CGT products for human use. If this is not the case, additional information on the manufacturing and/or testing may be needed to evaluate the quality of the raw material. The extent of testing required will depend on the specific raw material risks and the manner in which it is used in the CGT manufacturing process.
- For raw materials of other quality grade (i.e., non-authorized or non-compendial raw materials), a more extensive qualification and testing may be necessary. The risks of using research grade materials (including the risks to the continuity of supply) should be understood and evaluated whenever they are used. Additionally, the suitability of such raw materials for the intended use should be ensured, including – where appropriate – by means of testing (e.g., functional test, safety test). As a part of raw material qualification and assessment of suitability, the CGT product manufacturer should establish written procedures describing the handling, review, acceptance, and control of materials used in the manufacture.

6. Examples of Unique Challenges of Commonly Used Raw Materials

a. Sera from human or animal sources and serum replacements may introduce adventitious agents into the manufacturing process. TSE/BSE is a potential risk associated with bovine sera and therefore it is important to document the country of origin and starting source material type (e.g., whole blood, plasma). Additionally, sera are associated with a risk of viral adventitious agents and preferably should be gamma-irradiated (USP<1024>, Ph. Eur.5.1.1). Moreover, sera, whose exact composition is not always possible to define, have the potential of impacting product variability by affecting the reproducibility of the CGT manufacturing process or the quality of the DP. Special attention should be given to verifying the consistency of serum lots. For example, differences among serum lots used for cell culture may impact cell growth rate or differentiation potential. On the other hand, it is recommended to limit the number of donors used to donate the sera or plasma with respect the inherent risk of transmitting infectious agents from pooled sera or plasma and requirements on traceability.

b. Proteins produced by recombinant DNA technology have different contamination risks depending on the production system (e.g., bacteria, yeast, mammalian cells, or insect cells). When reusable chromatography columns are used in purification of proteins, it is important to ensure that cleaning procedures are adequate. The risk of contamination is reduced

through processing (e.g., viral reduction) and/or testing. Special attention should be paid when using antibodies generated from mouse hybridomas for the purification of proteins by affinity chromatography, which may introduce rodent viruses. For raw materials produced on animal or human cell lines, the CGT manufacturer should take into consideration data available on cell bank system testing, viral validation studies, viral safety data for unprocessed bulk, and estimation of viral safety residual risk/dose in the respective raw material. Raw materials free of carrier-proteins (proteins used as stabilizers) or raw materials of pharmaceutical grade are recommended, as the use of carrier-proteins may increase the risk of introducing adventitious agents. Lot-to-lot variability is also a considerable challenge, which should be addressed through qualification of each lot for its intended use.

c. Autologous or allogeneic cells or tissues used as raw material in CGT manufacturing (e.g., feeder layers or antigen presenting cells) should be qualified. Additionally, cells/tissues should be tested for adventitious agents including human-specific pathogens according to a careful risk assessment. Generally, the same safety requirements (including donor eligibility testing) as for human cells used as starting materials are applicable to human cells used as raw materials. Careful risk assessment should be used to define their quality profile considering also their processing and subsequent usage in the CGT manufacturing. The cells should be gamma-irradiated and tested for proliferation incompetency, unless otherwise justified. Cell banking and qualification of the cell banks may be helpful for quality control of cells as raw material.

d. When using antimicrobial agents in the manufacture of CGT products, bacteriostasis and fungistasis studies should be performed using a sample from the CGT product to demonstrate that the use of antibiotics does not interfere with the sterility testing, and that they are not present in the finished CGT product. In addition, because some patients may be sensitive to penicillin, beta-lactam antibiotics should be avoided in manufacturing of CGT products.