

Project - Hub Life Science – Advanced Therapy (LSH-TA) PNC-E3-2022-23683269 - funded by the Ministry of Health as part of the National Complementary Plan for the Innovative Health Ecosystem

CUP Code E83C22006230001

Technical Specifications for the provision of the service Quote Type: Cell Line Characterization, Modality: Viral Gene Therapies

For research activities at the Tumor Gene Therapy Research Unit, part of the Oncohematology Research Area, the Bambino Gesù Children's Hospital (OPBG) requests BioReliance Ltd. (hereinafter the Company) to provide cell line characterization services, according to standard protocols and standard reports in accordance with GMP regulations, with the aim of releasing a 3T3 mouse embryonic fibroblast cell bank to be used as a feeder layer in the production of a gene therapy product indicated for the treatment of patients affected by recessive dystrophic epidermolysis bullosa caused by loss-of-function mutations in the COL7A1 gene, which encodes type VII collagen, the constituent of the anchoring fibrils that ensure dermo-epidermal adhesion. The pharmaceutical product is based on the graft of autologous skin equivalents reconstituted in vitro, genetically corrected with a “self-inactivating” (SIN) retroviral vector expressing COL7A1, so as to induce the expression of C7 and consequent wound healing.

The 3T3 cell bank may be used in the aseptic manufacturing process only after verifying its microbiological and virological safety in accordance with the following regulations and guidelines:

- European Pharmacopoeia 11.7 "Gene Therapy Medicinal Product for Human Use";
- European Pharmacopoeia 11.7, Chapter 2.6.16 "Tests for Extraneous Agents in Viral Vaccines for Human Use"
- European Pharmacopoeia 11.7, Chapter 5.1.7 "Viral Safety"
- ICH Guideline Q5A(R2).

Therefore, the following analytical services are specifically required:

1. 360195GMP.BUK THE TEST FOR THE ENDOTOXIN

2. 032930GMP.BUK Detec of Vir Contam in Bovine Serum acc to EP, CPMP & US 9CFR Reqs

3. 005071GMP.BUK Presence of inapp vir using suckling mice, adult mice and embryonated eggs Acc FDA CBER Guidance

4. 102063GMP.BUK Test for presence of Agar-cultivable & Non Agar-cultivable Mycoplasma (USP, EP, 1993 PTC) w/o Avian Contr

5. 020000AGMP.BUK 020000AGMP.BUK for adherent cell expansion

6. 102062GMP.BUK Qualification of the test article for detection of mycoplasma in accordance

with USP/EP/PTC/JP

7. 705320GMP.BSV Short Tandem Repeat (STR) DNA Amplification and Analysis

Packaging

Packaging and wrapping must be disposable.

The packaging that constitutes each package must also be sturdy, made using the most suitable material for both the nature of the goods and the chosen shipping method, and must guarantee the final integrity of the delivered products. A label containing the following information must be affixed to the packaging:

- Supplier's identification mark;
- Name of the materials contained;
- Quantity expressed in the unit of measurement specific to the product;
- All information and labels required by law.

Any warnings or special precautions regarding storage must be in Italian and clearly legible. If the packaging or product wrapping does not comply with the instructions or shows defects, tears, or signs of tampering, the goods will be rejected and the Company will replace them at its own expense within the timeframes established for emergency deliveries. Packaging must be made of easily recyclable material or from renewable resources. Packages must be perfectly aligned, without overflowing, and bear the product information and packaging printed on the outside (either on the carton or on a self-adhesive label attached to the carton), which must be maintained at all times for the duration of the supply. The pallets on which the delivered products will be transported must be collected by the carrier at no charge to the Hospital.

Delivery methods of the supply

Delivery of the supplies is understood to include all costs related to packaging, transportation, portage, and delivery and must take place at the locations, times, and quantities indicated from time to time in the Purchase Order (PO). The Hospital's Cancer Gene Therapy Research Unit must be notified in writing of the actual delivery date. Deliveries must be made to the Pharmaceutical Factory Warehouse floor, Viale F. Baldelli 38, 00146 Rome.

Rejected goods will be made available to the Company for collection. The Company will be responsible for any damage resulting from deterioration of the unclaimed goods, as well as for collection transportation costs. If the goods are not collected by the Company within 15 (fifteen) days of notification, the Hospital will return the rejected products, charging the shipping costs. In the event of non-compliant supplies, the goods will be returned immediately. After five "non-compliant" supplies, the Hospital reserves the right to terminate the supply relationship. Proof of delivery of the products must be provided in duplicate on the transport document, which must state:

- recipient;
- delivery date and place;
- order number and date;
- detailed list of delivered materials (quantity, codes, description);
- quantity of material per batch;
- expiration date of individual products;
- production batch number of individual products;
- total number of packages/number of pallets.

At the time of delivery, products must have a residual shelf life (the period between the production date and the expiration date) of at least 2/3 (two-thirds). Otherwise, acceptance of the goods will be subject to the Hospital's discretion and, in any case, to the authorization of the Hospital's Innate Immunity Lymphoid Cell Research Unit, which must be informed in advance and must accept delivery of material with an expiration date different from the above.

At the time of delivery, products must be accompanied by analytical and conformity/analysis certificates for each manufacturer batch.

The Company must ensure, even during transport, compliance with the storage conditions for the supply. Where the storage temperature differs from the transport temperature, a stability document or equivalent declaration must be provided to allow acceptance of the material.

Acceptance of the products by the staff of the Hospital's Tumor Gene Therapy Research Unit does not exempt the Company from being responsible for any disputes that may arise when the product is used.

Should this occur, the Hospital's Cancer Gene Therapy Research Unit may request their immediate replacement at no additional cost. Failure to do so will be considered a "failure to deliver."

Dr. Christiane Hill

Odenthal, September 22nd