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Proposal
R-10455064.P.5
GMP Biopharmaceutical Facility Ospedale Pediatrico Bambino Gesù IRCCS
GMP Bio-E83C22003170001-Rossana

To
Rossana Bugianesi
GMP Biopharmaceutical Facility Ospedale Pediatrico Bambino Gesù IRCCS
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Submitted By
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Issue Date:

20 Jun 2025

THE INFORMATION CONTAINED IN THIS PROPOSAL IS SUBJECT TO THE FOLLOWING RESTRICTIONS:

Data contained in all pages of this proposal shall not be used or disclosed, except for evaluation purposes.

This proposal is valid until 31 December 2025.

1. OBJECTIVE

The purpose of this study is lot release testing of the Sponsor's cell and supernatant samples in standard test methods 011824GMP.BUK and 009820GMP.BUK for the detection of Replication Competent Retrovirus (RCR) with the additional inclusion of RD-114 virus as an additional positive and spike control.

2. SCOPE OF WORK

Based on the preliminary information provided by GMP Biopharmaceutical Facility Ospedale Pediatrico Bambino Gesù IRCCS, the following are considered to be the estimated milestones of this project. The scope of the project and price may change upon receipt of additional information. Upon signature of the proposal as intent to move forward, Project Management will schedule a project kick-off meeting with GMP Biopharmaceutical Facility Ospedale Pediatrico Bambino Gesù IRCCS to review deliverables, requirements and timelines.

- **Compliance Level Definition Summary**

NRT or non-GxP	No QA Oversight; No Specification Required. NRT = Non-Regulatory Testing
GLP	QA Oversight; No Specification Required
GMP	QA Oversight; Specification Required. If no specification is provided, then results will be reported as "Report Results. For Information Only" or similar terms.
Development	All activities prior to validation or transfer. This may include assay design, optimization, feasibility assessment and robustness evaluation
Validation	Study to determine the performance characteristics of the fully developed assay inducted in accordance with ICH Q2 (R2) or other relevant regulations

Custom Method 1

- Assay code: 011824GMP.BUK

a. Lot release test will be performed on the Sponsor's cell bank using the 011824GMP.BUK assay ("Detection of Replication Competent Retrovirus (RCR) by co-cultivation with HEK293 cells (5 passages, PG4 S^+L^- end-point)").

b. This will include the standard assay positive and spike control using Gibbon Ape Leukemia Virus (GALV) inoculated at 100 Focus Forming Units (FFU)/ culture.

c. Additional single replicate RD-114 positive and spike controls inoculated at 100, 10, and 1 FFU/culture will be included for information purposes. This will be documented on a Technical Specification Amendment (to be approved by the Sponsor prior to initiation of each study).

d. RD-114 positive controls will also be included in the PG4 S^+L^- endpoint test for information purposes.

e. Regulatory Requirement:

- GMP

f. Deliverables to GMP Biopharmaceutical Facility Ospedale Pediatrico Bambino Gesù IRCCS:
   - Technical Specification Amendment detailing the additional controls for each study
   - Certificate on Analysis for each study

g. Requirement from GMP Biopharmaceutical Facility Ospedale Pediatrico Bambino Gesù IRCCS:
   - Approval of Technical Specification Amendment for each study
   - Sufficient cryopreserved cells to inoculate each study. The regulatory guidance is to test 1% of the total cells produced or 1 x 10^8 cells, whichever is less. The number of cells required for testing will depend on Sponsor requirements, however, should include additional material for the standard GALV spike control and additional RD-114 spike controls (e.g. an additional 4 x 10^7 cryopreserved viable cells may be required, based on testing 1 x 10^7 test article cells/ culture).
   - Sufficient back-up sample for repeat testing, if required.

h. If further development is required, we will work with GMP Biopharmaceutical Facility Ospedale Pediatrico Bambino Gesù IRCCS to determine the scope of that work and generate a new proposal, an amendment to this proposal or a quote.

Custom Method 2

- Note: Custom Method 2 may be performed in parallel with Custom Method 1
- Assay code: 009820GMP.BUK

a. Lot release test will be performed on the Sponsor's supernatant sample using the 009820GMP.BUK assay ("Detection of Replication Competent Retrovirs (RCR) by inoculation on 293 detector cells (5 passages, PG4 S+L- end-point)").

b. This will include the standard assay positive and spike control using Gibbon Ape Leukemia Virus (GALV) inoculated at 100 Focus Forming Units (FFU)/ culture.

c. Additional single replicate RD-114 positive and spike controls inoculated at 100, 10, and 1 FFU/culture will be included for information purposes. This will be documented on a Technical Specification Amendment (to be approved by the Sponsor prior to initiation of each study).

d. RD-114 positive controls will also be included in the PG4 S^+L^- endpoint test for information purposes.

e. Regulatory Requirement:
   - GMP

f. Deliverables to GMP Biopharmaceutical Facility Ospedale Pediatrico Bambino Gesù IRCCS:
   - Technical Specification Amendment detailing the additional controls for each study
   - Certificate on Analysis for each study

g. Requirement from GMP Biopharmaceutical Facility Ospedale Pediatrico Bambino Gesù IRCCS:
   - Approval of Technical Specification Amendment for each study
   - Sufficient sample to inoculate each study. The regulatory guidance it to test 5% of the total material produced. The volume of sample required will depend on Sponsor requirements, however, should include additional material for the standard GALV spike control and additional RD-114 spike controls (e.g. an additional 200 ml may be required, based on testing 50 ml of test article/ culture)
   - Sufficient back-up material for repeat testing, if required.

h. If further development is required, we will work with GMP Biopharmaceutical Facility Ospedale Pediatrico Bambino Gesù IRCCS to determine the scope of that work and generate a new proposal, an amendment to this proposal or a quote.

➢ **Routine Assays**

Assay	Description	Qty	Total Price (EUR)
MCB			
020000GMP.BUK	CELL GROWTH AND SAMPLE PREPARATION (GMP)	1	€ 2,809.15
305400GMP.BUK	Real Time PCR for the Detection of Porcine circovirus (PCV) in Biological Samples	2	€ 12,011.80
032930GMP.BUK	Detec of Vir Contam in Bovine Serum acc to EP, CPMP & US 9CFR Reqs	2	€ 26,497.40
011824GMP.BUK	RCR Co-cult (293 Cells, 5 Passages, PG4 S+L- End-point) - Between 1.25x10^7 and 1x10^8 cells	2	€ 43,418.00
033970GMP.BUK	In Vitro for detection of Porcine Viral Contaminants using PPK and Vero DCL	2	€ 50,707.20
003000GMP.BUK	Extended In vitro (Incorporating day 14 passage) for detec of viral contaminants 6WP using 3DCL	2	€ 36,016.40
360195GMP.BUK	LAL TEST FOR THE ENDOTOXIN (QUANTITATIVE	2	€ 2,612.50
305518GMP.BUK	QPCR for the Detection of Human Papilloma Virus (HPV) DNA	2	€ 28,268.20
510636GMP.BUK	Qualification for sterility Testing by Direct Inoculation Method (EP, USP and JP)	2	€ 4,218.00
102062GMP.BUK	Qualification of the test article for detection of mycoplasma in accordance with USP/EP/PTC/JP	2	€ 13,248.70

013013GMP.BUK	TEM for detection of contaminants (200 profiles)	2	€ 20,533.30
305500GMP.BUK	Qualitative Polymerase Chain Reaction (PCR) Assay for Detection of PINNACLE HUMAN PANEL	2	€ 76,541.50
305519GMP.BUK	Polymerase Chain Reaction Assay for the Detection of Human Polyomavirus (HPyV) in Biological Samples	2	€ 36,286.20
305530GMP.BUK	Real Time Quantitative Polymerase Chain Reaction Assay for the Detection of Human Enterovirus (hEV)	2	€ 14,464.70
705320GMP.BSV	Short Tandem Repeat (STR) DNA Amplification and Analysis	2	€ 12,361.40
102063GMP.BUK	Test for presence of Agar-cultivable & Non Agar-cultivable Mycoplasma (USP, EP, 1993 PTC) w/o Avian Contr	2	€ 7,411.90
005071GMP.BUK	Presence of inapp vir using suckling mice, adult mice and embryonated eggs acc FDA CBER Guidance	2	€ 49,707.80
PPCB			
020000UGMP.BUK	CUSTOM CELL GROWTH AND SAMPLE PREPARATION (GMP)	3	€ 11,113.20
360195GMP.BUK	LAL TEST FOR THE ENDOTOXIN (QUANTITATIVE)	3	€ 3,918.75
510636GMP.BUK	Qualification for sterility Testing by Direct Inoculation Method (EP, USP and JP)	3	€ 6,327.00
032930GMP.BUK	Detec of Vir Contam in Bovine Serum acc to EP, CPMP & US 9CFR Reqs	3	€ 39,746.10
011824GMP.BUK	RCR Co-cult (293 Cells, 5 Passages, PG4 S+L- End-point) - Between 1.25x10^7 and 1x10^8 cells	3	€ 65,127.00
020102GMP.BSV	Cell Line Morphology Study	3	€ 12,349.05
033970GMP.BUK	In Vitro for detection of Porcine Viral Contaminants using PPK and Vero DCL	3	€ 76,060.80
003000GMP.BUK	Extended In vitro (Incorporating day 14 passage) for detec of viral contaminants 6WP using 3DCL	3	€ 54,024.60
102062GMP.BUK	Qualification of the test article for detection of mycoplasma in accordance with USP/EP/PTC/JP	3	€ 19,873.05
705320GMP.BSV	Short Tandem Repeat (STR) DNA Amplification and Analysis	3	€ 18,542.10

102063GMP.BUK	Test for presence of Agar-cultivable & Non Agar-cultivable Mycoplasma (USP, EP, 1993 PTC) w/o Avian Contr	3	€ 11,117.85
005071GMP.BUK	Presence of inapp vir using suckling mice, adult mice and embryonated eggs acc FDA CBER Guidance	3	€ 74,561.70
Retroviral vector			
032930GMP.BUK	Detec of Vir Contam in Bovine Serum acc to EP, CPMP & US 9CFR Reqs	3	€ 39,746.10
016005GMP.BSV	Detection and Measurement of 293 (Human Embryonic Kidney) Host Cell Protein by Enzyme Immunoassay	3	€ 4,659.75
009820GMP.BUK	RCR Infectivity (293 Cells, 5 Passages, PG4 S+L- End-point) - Between 100ml and 250ml as TA	3	€ 53,853.00
003000GMP.BUK	Extended In vitro (Incorporating day 14 passage) for detec of viral contaminants 6WP using 3DCL	3	€ 54,024.60
430026GMP.BSV	OSMOLALITY DETERMINATION USP 785	3	€ 3,591.00
102062GMP.BUK	Qualification of the test article for detection of mycoplasma in accordance with USP/EP/PTC/JP	3	€ 19,873.05
300511GMP.BUK	Quantitative Polymerase Chain Reaction of HEK293 Host cell gene Targets, E1A and E1B	3	€ 26,966.70
102063GMP.BUK	Test for presence of Agar-cultivable & Non Agar-cultivable Mycoplasma (USP, EP, 1993 PTC) w/o Avian Contr	3	€ 11,117.85
003006GMP.BUK	Evaluation to Determine CytoToxicity of Test Articles Prior to an In vitro Assay	2	€ 8,990.80
		Total:	**€1,052,698.20**

3. PROJECT WORKFLOW AND TIMELINE ESTIMATES

Upon signature of this proposal and receipt of a valid purchase order, BioReliance® Services Project Management will review capacity with operational leaders to determine actual timelines. BioReliance® Services Project Management will then generate a project plan/timeline to be reviewed and agreed to with the Client at a project kick-off meeting.

4. PROJECT PRICE

Description	Assay Number	QTY	Price (EUR)
Project 1, Routine Assays	Various Methods	See Above	€1,052,698.20
		Total:	**€1,052,698.20**

5. PAYMENT TERMS

Unless superseded by a separate, signed written agreement between BioReliance® Services and the Client, invoices shall be paid in accordance with the following terms, contingent on a satisfactory credit review:

Project 1, Routine Assays	55% invoiced upon order booking
	20% invoiced upon lab initiation
	25% invoiced upon order completion should the order complete on or prior to 31st December 2025*

* Should the order be ongoing after 31st December, 15% will be paid as a partial payment against the final invoice and the remaining 10% paid upon completion

Unless otherwise in writing by BioReliance® Services, payment shall be due **net 30** from the date of the invoice.

6. CLIENT CONTACTS

- **GMP Biopharmaceutical Facility Ospedale Pediatrico Bambino Gesù IRCCS point of contact for this project will be:**

Rossana Bugianesi
Quality Control Manager
+39 06 68597202
rossana.bugianesi@opbg.net

7. PROJECT CONTACTS

- **BioReliance® Services' project points of contact for this project will be:**

Dr. Christiane Hill
Account Manager
christiane.hill@merckgroup.com

8. CANCELLATIONS

Unless superseded by a separate, signed written agreement between BioReliance® Services and GMP Biopharmaceutical Facility Ospedale Pediatrico Bambino Gesù IRCCS, the following cancellation fee schedule will apply to each Project:

Cancellation <2 weeks before planned Lab Initiation date of any Milestone:	20% of the total price of applicable Milestone(s)
Cancellation after Lab Initiation of any Milestone:	50% of applicable Milestone(s)
Cancellation after Lab Completion of any Milestone:	90% of applicable Milestone(s)

9. REPEATS

Repeat testing may be subject to additional charges to GMP Biopharmaceutical Facility Ospedale Pediatrico Bambino Gesù IRCCS. Prior to initiating any work, including repeat testing, considered out of scope for this proposal, our Project Management or Account Manager will review with GMP Biopharmaceutical Facility Ospedale Pediatrico Bambino Gesù IRCCS and issue a quotation and/or proposal amendment.

10. RISK ASSESSMENTS AND SAFETY

Any known safety hazards associated with the test articles or reagents supplied for use in these studies must be reported to BioReliance® Services in order to allow a full risk assessment of the study to be conducted. Please be aware that there may be a requirement for licences to import and/or handle certain biological or infectious materials, and it is essential that these be in place before shipment of materials is arranged. Please note that no work shall commence until all relevant risk assessments and licences are in place.

Please also note that for studies under consideration at our UK facilities, BioReliance® Services is required by the UK Health and Safety Executive under European Commission Directive 94/51/EC to have a risk assessment of any GMO present in its facility. Therefore, if the material to be supplied is classified as a Genetically Modified Organism (GMO), we request that you inform us of the safety assessment for the test article. Alternatively, if requested by you, BioReliance® Services' own Genetic Safety Committee can do an assessment for you.

11. REGULATORY AND LEGAL NOTICES

Unless otherwise stated or expressly requested, this study will be conducted in laboratories compliant to GLP and GMP.

Any changes to the scope of this study including, but not limited to design, performance, materials and/or equipment are subject to the BioReliance® Services change control process, which may result in additional cost to the Client.

For method transfer projects, BioReliance® Services will endeavor to use the same critical reagent material as highlighted by the Client's SOP/Method/Protocol. However, if the supplier is not an approved vendor by the BioReliance® Services Quality Assurance Department, it will be the responsibility of the Client to provide the supplier quality details to confirm the reagent is acceptable for GxP use.

The pricing information provided in this proposal is the best estimate by BioReliance® Services based on the details available at this time. The price may vary upon further investigation by BioReliance® Services and additional information provided by the Client, prior to commencing the study.

Unless expressly stated herein, neither party grants nor implies the transfer of any Intellectual Property to the other party as a result of this contract. All data and results generated in this study are confidential and are owned solely by the Client. All data and results generated in this study will not be shared with any other entity without first receiving written permission from the Client.

BioReliance® Services is and shall continue to be the sole owner of, all concepts, inventions, improvements, designs, programs, formulas, know-how, methods, processes, and writings utilized or developed in conducting the Project to the extent relating solely and generally to the business, processes, practices, or services performed by BioReliance® Services for its customers.

If, in the course of providing the Services, Client requests and BioReliance® Services agrees to develop or make any improvement, design, process, documents or other material, the parties will reduce the agreement to writing in a contractual form, such as this Proposal or

subsequent Individual Project Assignment (IPA), including the compensation to be paid for such developments. The copyrights, patent and all other intellectual property rights, and all legal and beneficial right, with and interest therein shall be identified therein; all other intellectual property developed by BioReliance® Services, in the course of providing the Services, shall belong to BioReliance® Services.

12. TERMS & CONDITIONS

Except to the extent superseded by a separate signed written agreement (i.e., a negotiated Master Service Agreement) between BioReliance® Services and GMP Biopharmaceutical Facility Ospedale Pediatrico Bambino Gesù IRCCS, the Services described in this quotation will be governed by the relevant BioReliance® Services' Statement of Terms and Conditions, which are included herewith, or incorporated herein by reference:

Testing and Storage Terms and Conditions

13. SIGNATURES

We require a hard copy of a valid Purchase Order or equivalent prior to the initiation of the work quoted. If there will be delay in processing the PO, a signature is required below by an authorized company representative. At your earliest convenience, a hard copy should be scanned and forwarded to our Account Manager and/or Project Manager before testing is scheduled for completion.

If a Purchase Order will not be provided, please sign and complete a billing and shipping information form (provided separately) to ensure correct mailing of the invoices and reports/CofAs.

Signed on Behalf of:

GMP Biopharmaceutical Facility Ospedale Pediatrico Bambino Gesù IRCCS:

Signature

Name

Title

Date

Client PO Number

Signed on Behalf of:

BioReliance Ltd:

Signature

Dr. Christiane Hill

Name

Account Manager

Title

29 July 2025

Date

Confidentiality

This document has been prepared by and remains the sole property of BioReliance Ltd. It is submitted to GMP Biopharmaceutical Facility Ospedale Pediatrico Bambino Gesù IRCCS solely for use in evaluating BioReliance Ltd qualifications and/or quotations concerning the particular projects for which it was prepared. This document is confidential to BioReliance Ltd and GMP Biopharmaceutical Facility Ospedale Pediatrico Bambino Gesù IRCCS agrees to treat the document in accordance with the terms of any Confidentiality Agreements previously signed and, in any event, shall not disclose to any third party without the consent of BioReliance Ltd not to be unreasonably withheld.