INSTRUCTIONS FOR TENDERERS

1. GENERAL INFORMATION

1.1. Procurement identification number: CBL-2026-1.

1.2. **Contracting Authority: Limited Liability Company "Cellboxlab"**, Reg. No. 42103111196, ddress: Ataru ceļš 42, Atari, Ādaži parish, Ādaži municipality, LV-2164.

1.3. The procurement **"Digital Twin development"** is carried out according to Cabinet Regulation No.104 within the EU-funded project **"Leveraging Digital Twin and Gut-on-a-Chip Models for Precision Metformin Dosing in Type 2 Diabetes Patients (DIGI-MET2D), No. 1.1.1.3/1./24/A/043**.

1.4. **Tenderer** – supplier submitting a tender.

1.5. **Tender** – the tender submitted within procurement CBL-2026-1.

1.6. **Supplier** – natural/legal person or an association thereof offering services.

1.7. **Subject: "Digital Twin development"** (the Service).

1.7.1. Execution deadline: indicated in Annex 1 – Task Description.

1.7.2. A Tenderer may submit one tender, covering the entire scope. Evaluation is based on total price (excluding VAT).

1.8. Information and clarification:

1.8.1. The contact person authorized to provide organizational information regarding the procurement procedure and these Instructions is: Ieva Jokste, e-mail: ieva.jokste@cellboxlabs.com.

1.9. Tender submission and opening procedure:

1.9.1. Deadline: **28 January 2026, 13:00 CET**, electronically by email ieva.jokste@cellboxlabs.com.

1.9.2. Modifications of the tender allowed until deadline.

1.9.3. Evaluation and verification of the qualification will be performed in closed Committee sessions.

2. PREPARATION OF THE TENDER

2.1. Requirements:

2.1.1. Financial offer and Qualification documents must be submitted electronically.

2.1.2.Secure electronic signature permitted.

2.1.3.The financial offer must be submitted in Latvian or in English only. Qualification documents (for example, certificates) must be submitted in Latvian or English; they may be submitted in another language if accompanied by a translation into Latvian certified by the Tenderer.

2.1.4.Submission confirms acceptance of all requirements.

2.2. Documents to be submitted:

2.2.1.Financial offer (Annex 2).

2.2.2.Qualification documentation.

3. EXCLUSION RULES

3.1. Exclusion per Cabinet Regulation No.104 Article 12.

3.2. Exclusion shall apply in cases of insolvency, liquidation, or suspension of economic activity.

3.3. Exclusion under International and National Sanctions Law Paragraph one and two of Article 11.[1].

4. QUALIFICATION REQUIREMENTS

4.1. Tenderer must meet the following requirements:	4.2. Tenderer must submit the following proof:
Compliance with professional activity	Compliance with professional activity
4.1.1. Registered according to national legislation.	4.2.1. To verify compliance with Section 4.1.1 of the Regulations regarding the registration of a Tenderer in the Republic of Latvia in accordance with the requirements of regulatory enactments, the Commission shall check the databases of The Register of Enterprises of the Republic of Latvia or the State Revenue Service. Non-resident Tenderers shall submit a document certifying their registration, except in cases where such information is available in a public database.
4.1.2. At least 1 (one) study in last 5 (five) years developing Digital Twin of MPS.	4.2.2. To confirm compliance with Section 4.1.3 of the Regulations, the Tenderer shall attach a list of references of completed studies/projects.
4.1.3. Specialist(s) must have required experience:	
4.1.3.1. Specialist led at least 2 (two) studies involving Digital Twin Development in last 5 (five) years.	4.2.3.1. To confirm compliance with Section 4.1.3.1 of the Regulations, the Tenderer shall attach CV with listed studies.

5. VERIFICATION OF OFFERS FORMATTING, VERIFICATION OF FINANCIAL OFFER AND SELECTION OF APPLICANTS

5.1. The commission verifies the formatting of offers and makes selection of Applicants in the closed meeting, during which the Commission checks the compliance of offers to the requirements stated in the Instruction and verifies the compliance of Applicants to the requirements stated in Section 3 of the Instruction.

5.2. The offer of Applicant is declined and is not subjected to the further verification, if the commission states that:

5.2.1. The offer of Applicant had discrepancy to the requirements stated in Section 2 of the Instruction, a complete set of the offer is not submitted that does not allow to identify the Applicant and content of the offer.

5.2.2. The Applicant does not comply or has not indicated the compliance to any of the requirements stated in Section 4 of the Instruction.

5.3. Commission performs the verification of the Financial offer.

5.4. Contractor executes negotiations with the Applicant, who has submitted the lowest total contract price and whose offer complies with the requirements stated in Section 5.1 and 5.2 of the Instruction in order to ascertain the compliance of the Applicant with the qualification requirements stated in Section 4 of the Instruction as well as confirm the comprehension on performable work assignments.

5.5. If the Applicant during the negotiations expresses certainty on its ability to provide the Service, it is decided to conclude the Contract with the Applicant. If the Applicant during the negotiations the Applicant is not able to ascertain the Commission on the ability to perform the work or the Parties do not agree on the Contract conclusion due to other reasons, the Applicant, who has provided the next lowest total contract price, is invited to the negotiations.

6. AWARD OF THE CONTRACT RIGHTS, CONTRACT CONCLUSION

6.1. The Commission considers as winner the Applicant, who is chosen according to the requirements and criteria stated in the Instruction and is no excludable from participation in the Tender according to the Sections 3.1, 3.2 and 3.3. of the Instruction.

6.2. The Contractor informs all the Applicants on the decision about the Applicant or the Applicants selected within the Tender within three working days after the decision is made and provides them with the information specified in the decision or sends the mentioned decision to them;

6.3. The Contractor concludes the contract according to the Instruction and the Applicant offer.

7. PERSONAL DATA PROCESSING

7.1. The Contractor will process the personal data submitted in the Tender, will store the Tender documents and will transfer the personal data to the Procurement Monitoring Bureau and/or the Official Journal of the European Union and/or the Central Finance and Contracting Agency and/or other institutions involved in the management of European Union funds and/or the Administrative District Court, in accordance with the requirements stated in the Public Procurement Law, the regulatory enactments governing the management of European Union funds, Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 On the protection of natural persons with regard to the processing of personal data and on the free movement of such data and other applicable regulatory enactments.

8. ANNEXES

8.1. Annex 1 – Task Description
8.2. Annex 2 – Financial Offer

ANNEX 1 – TASK DESCRIPTION

Task 1 – Development of a human Digital Twin for metformin pharmacokinetics

The contractor shall develop a physiologically based pharmacokinetic (PBPK) "human digital twin" model describing metformin pharmacokinetics, using the patient dataset selected by Tenderer and supported by published clinical and mechanistic evidence. The contractor will be required to:

1. **Develop a PBPK model of metformin** using qualified installations of PK-Sim (Version 12), incorporating:
    - Physiological and biochemical parameters derived from the OPTIMED cohort,
    - Relevant mechanistic data from peer-reviewed publications,
2. **Perform computational pre- and post-processing** using R (version 4.0) and RStudio (version 1.2.5) where applicable, following standard analytical procedures for PBPK model development and evaluation [PMID: 27653238].
3. **Ensure compliance with international guidelines** governing PBPK modelling and reporting, including:
    - EMA guideline on PBPK Modelling and Simulation (2019),
    - Relevant FDA and/or OECD guidance documents.
4. **Qualify the PBPK model** against available clinical pharmacokinetic data to ensure predictive accuracy and mechanistic plausibility.
5. **Simulate personalised pharmacokinetic profiles** incorporating patient-specific variables such as:
    - Renal function,
    - Hepatic enzyme activity,
6. **Microbiota-mediated drug interactions**, if applicable and data permits parameterization of relevant model variables.
7. **Generate concentration profiles** that will be used to define physiologically relevant metformin exposure ranges for subsequent in vitro testing.

The contractor is expected to deliver a fully qualified PBPK model, documentation of assumptions and model parameters, and simulation outputs suitable for informing experimental design in downstream project tasks.

Task 2 – Development of a Digital Twin of the Gut on Chip (GoC) for metformin dosage optimization

The contractor shall develop a digital twin (DT) model of the GoC system to simulate metformin concentration kinetics within the microfluidic environment. The contractor will be required to:

8. **Develop a mathematical GoC digital twin model** that incorporates:
    - Hardware-specific parameters (e.g., media volumes, flow rates, chip geometry),
    - Physico-chemical properties of metformin,
    - Relevant biological processes, including permeability across the membrane and cell layers.
9. **Generate on-chip pharmacokinetic simulations** to identify metformin dosing conditions that reproduce kinetic profiles comparable to the personalised human digital twin simulations produced under Task 1.
10. **Integrate experimental measurement data** from GoC assays by adjusting kinetic parameters to achieve mechanistic alignment between model outputs and observed data.
11. **Estimate permeability and other distribution-related parameters** (e.g., partitioning into the cellular compartment) by:
    - Defining an appropriate cost function representing the squared difference between model simulations and biological measurements,

- Applying automated parameter - fitting algorithms to minimise the cost function and refine the DT model.

12. **Ensure model reproducibility and documentation**, providing transparent reporting of:
    - Input parameters,
    - Assumptions,
    - Calibration results,
    - Model performance metrics.

The contractor is expected to deliver GoC digital twin capable of predicting on-chip metformin kinetics and supporting dosage optimisation for downstream experimental work.

Task 3 – GoC Digital Twin for metformin kinetics and companion biomarker correlation

The contractor shall utilise the GoC DT developed under Task 2 to simulate metformin kinetics within the microfluidic environment and to correlate on-chip drug exposure profiles with relevant biological biomarkers. The contractor will be required to:

13. **Perform GoC digital twin simulations** to reproduce metformin concentration–time profiles under physiologically relevant conditions, reflecting the dosage scenarios identified in Task 3.
14. **Correlate simulated drug exposures with biological biomarkers**, including:
    - Toxicity indicators (e.g., epithelial damage, inflammatory readouts),
    - Dose–response relationships,
    - IC_{50} or equivalent metrics derived from GoC experimental data.
15. **Analyse inter-individual variability** by incorporating clinical outcome information from the OPTIMED cohort, with particular focus on:
    - Patients identified as metformin-intolerant,
    - Patients classified as non-responders,
    - Individuals presenting adverse effects potentially linked to gastrointestinal or microbiota-mediated mechanisms.
16. **Simulate the impact of varying metformin dose levels** directly within microbiota-containing GoC environments to:
    - Identify personalised effective dose ranges,
    - Determine thresholds for non-toxic and clinically relevant exposure levels,
    - Support optimisation of individual dosing strategies.
17. **Interpret the results to enhance mechanistic understanding** of the relationship between:
    - Metformin pharmacokinetics,
    - Host gastrointestinal responses,
    - Microbiota-driven modulation of drug efficacy and intolerance.

The contractor is expected to deliver model outputs, dose–response analyses, biomarker correlations, and a summarized interpretation suitable for integration with downstream experimental and modelling tasks.

Task 4 – Validation of selected metformin dose using Digital Twin simulations

The contractor shall validate the selected metformin dose through integrated digital twin (DT) simulations, combining outputs from the GoC digital twin and the PBPK models developed in Task 1. The contractor will be required to:

18. **Integrate GoC DT and PBPK model outputs** to simulate metformin pharmacokinetics and evaluate predicted in vivo toxicity profiles for the proposed dose levels.
19. **Conduct in silico simulations for clinical situations** focusing on:
    - Patients identified as metformin-intolerant,
    - Identification of personalised, effective, non-toxic dose ranges,

    - Assessment of dose adjustments required to mitigate intolerance.
20. **Perform personalised efficacy assessments** for each intolerant patient by incorporating multimodal datasets (e.g., omics, faecal microbiome profiles, and other biological readouts) as identified in Task 3, with the goal of refining predictions of individual treatment responses.
21. **Quantify inter-patient variability in dose response** using appropriate statistical and computational approaches, including:
    - Bayesian hierarchical modelling,
    - Sensitivity analysis and uncertainty quantification,
    - Comparative evaluation of predicted toxicity thresholds.
22. **Provide a personalised dosing framework** suitable for supporting downstream experimental confirmation and clinical translation activities.

The contractor is expected to deliver validated simulation results, documentation of modelling assumptions, and a summary of personalised dosing recommendations derived from integrated digital twin analyses.

DELIVERABLES
T1 Deliverable: Qualified human digital twin (PBPK) model of metformin
T2 Deliverable: Digital twin of the Gut-on-a-Chip
T3 Deliverable: Development and description of patient specific GoC DT and correlations with possible companion biomarkers
T4 Deliverable: *in silico* simulations of various dosing schemes for metformin-intolerant patients

Deliverables must be submitted only in Latvian or English.

PAYMENT SCHEDULE
1) First advance payment: 50% after contract signing.
2) Second advance payment: 20% after completion of Tasks 1 and acceptance of deliverables, but no later than 30 days after Task 1 deadline.
3) Third advance payment: 20% after completion of Tasks 2 and acceptance of deliverables, but no later than 30 days after Task 2 deadline.
4) Last payment: 10% after completion of Tasks 3 and Tasks 4 acceptance of deliverables, but no later than 30 days after Task 4 deadline.

DEADLINES
Task 1 – Till 31 March, 2026
Task 2 - Till 30 November, 2026
Task 3 – 4 – Till 31 March, 2027

ANNEX 2

FINANCIAL OFFER

Tenderer name	
Registration number	
Legal address	
Email	
Contact person	
Phone	
Contact email	
Bank name	
Bank code	
Account number	
Contract signer (name, position)	
Service	
Total excl. VAT	
VAT	
Total	

By submission of this offer, the Applicant approves that:

- *It applies to participate in the tender process "Digital Twin development" (No CBL-2026-1);*
- *The submitted Financial offer and the other documents included in the Offer are correct and include all the costs related to the Service provision; in no way is interested in any other offer and is not participating in any other offer, as well as has not performed any competition restricting activities in relation to the any other offer submitted within the Tender;*
- *The information and documentation included in its offer are complete and truthful;*
- *It has reviewed all the documents of this Instruction and fully understands the terms and requirements of the Tender procedure;*
- *Al the current documents submitted in the offer of the Applicant are an integral part of this offer and are a binding part of this offer to the Applicant;*
- *All the necessary volumes and capacities of the financial, technological and human resources are at disposal of the Applicant in order to provide the execution of service in the stated terms and in excellent quality;*
- *The Service will be provided according to the Annex No. – Work Assignment;*
- *If the Purchaser will chose this service, we undertake to conclude the contract and fulfill all the contract requirements.*

_____

(Tenderer)

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(Authorized representative)

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(Signature)

_____

(Date)