Call Guidelines for the Codex4SMEs Biomarker validation service

The road from the discovery of a potential biomarker to its use in the clinic can be long, expensive and risky. Pre-clinical validation is an essential step towards the commercialisation of a biomarker. It allows the SMEs to objectively assess the potential clinical application of a biomarker and increases the chances to invest in the right product.

The Codex4SMEs (Companion diagnostics expedited for SMEs) project aims at improving healthcare by enhanced adoption of Personalized Medicine (PM) in NWE and beyond. Codex4SMEs provides a transnational network of nine partners and two sub-partners from seven countries (DE, FR, NL, UK, IE, LU and AT). The project supports SMEs along the Companion diagnostics (Cdx) value chain from the incubation to the growth catalyst.

The objective of the present call is to offer an additional valuable support to 4 SMEs in their efforts in moving towards the full validation of a biomarker. The selected SMEs will be provided with a robust proof-of-concept for their biomarker by a biomarker validation service resulting in a new product. More information on the Codex4SMEs project may be found on the Interreg NWE website[1].

IBBL (Integrated BioBank of Luxembourg) is the lead Biobank for the Biomarker validation Services within the Codex4SMEs project. IBBL is an autonomous not-for-profit institute dedicated to helping researchers bridge the gap between bench and bedside. To accelerate the translation of biomarkers into the clinic, IBBL has developed a biomarker validation service that takes biomarker candidates through the early stages of validation from discovery right up to clinical validation. IBBL's scientific leaders have many years of experience in biomarker validation and a track record of bringing products to market. Its team of experts ensures that the design and execution of biomarker validation studies is done to the highest standards. IBBL can carry out all the steps of pre-clinical validation including, pre-analytical and analytical validation, a clinical verification pilot study and a comparison to gold standards/reference methods.

Through the Biobank of Graz (BBG), one of the largest clinical biobanks in Europe with large collections of biological materials (about 20 million samples) both population-based and disease-focused, Codex4SMEs can provide access to sets of well-annotated human biospecimens and quality control material.

In the end, the four selected SMEs will receive a validation report and recommendations, which is a major step towards the Companion diagnostics production steps. The selected SMEs will also benefit from the support and networking opportunities offered by Codex4SMEs to decrease their time to market and improve their chance of success by boosting the Technology readiness level of the biomarkers.

Codex4SMEs invites innovative SMEs developing Companion diagnostics located in one of the five partner states (Germany, France, Netherlands, United Kingdom and Ireland) to propose their biomarker candidate(s) for validation. One SME may apply with one biomarker candidate only. Codex4SMEs will select four

candidates and offer to perform the pre-clinical validation at no cost to the company. There are a few conditions as set out below.

1. The agreement

For all applicants

- Non-Disclosure Agreement (NDA)

The Codex4SMEs Expert group as well as all involved partners and the Codex4SMEs consortium will sign an Non - Disclosure Agreement (NDA) protecting information and data gained from the applicants during the application and evaluation processes. Furthermore, the above mentioned parties will sign and agree not to use the applicant's idea.

Applicants have to agree to this procedure during the application process. Agreement to this procedure is given through the respective application form.

The applicants agree to complete the application form, including the self declaration of the State aids received by the company under the *de-minimis* rule accurately and truthfully.

- **Data Protection Regulation**

Data submitted to the regional partners of the Codex4SMEs consortium will be treated according to the EU Regulation 2016/679 (General Data Protection Regulation - "GDPR").

For the winners

Following evaluation and selection, the successful applicants ("the winners") will sign an agreement with the members of the Codex4SMEs based on the following principles:

- IBBL agrees to perform the biomarker validation service at no cost to the winners, including:
    - pre-analytical validation
    - analytical validation
    - a clinical verification pilot study (limited to 100 cases)
    - the provision of a report on the validation study with recommendations
- Biobank Graz (BBG) agrees to provide the biospecimen required for the biomarker validation service as far as these are available in the Biobank
- The Codex4SMEs partners agree to:
    - waive the right to any intellectual property related to the biomarker candidate
    - waive the right to any royalties from the commercialisation of the biomarker candidate
- The winners agree to:
    - sign a Non - Disclosure Agreement (NDA) with IBBL,

- acknowledge IBBL, BBG, where applicable, any other source of biospecimen and the Codex4SMEs partners in scientific publications and commercial brochures
- provide all information and documentation required to implement the biomarker validation plan in particular full details of the materials and methods to allow IBBL to establish the method on its own laborytory
- allow Codex4SMEs consortium to use the name of the winners for communication purposes
- provide a report, latest 1 month after the reception of the Biomarker validation report by IBBL

Note: Winners may use the name of Codex4SMEs, IBBL and BBG in their communications.

2. Eligibility & Technical Requirements

Applicants must meet all the eligibility and technical requirements below:

Eligibility

- SME based in Nord West Europe within one of the partners' regions (Germany, France, Netherlands, United Kingdom and Ireland).
- provide a self-declaration of the State aid received by the SME following the *de-minimis* rule, together with the application form. See the information at the end of the guidelines for more information on *de-minimis* regulation.

Technical Requirements

- Accepted class of biomarker:
  - protein/peptide
  - metabolite
  - DNA (human or bacterial)
  - RNA/miRNA

- Accepted analytical method:
  - immunoenzymatic assays
  - PCR/ qRT-PCR
  - immunohistochemistry
  - sequencing
  - flow cytometry

- The winners are expected to submit a complete analytical protocol for the implementation of the biomarker validation method.

3. Process & Timeframe

Two calls for proposals will be open:

Call opening	Expected call closure	Expected number of Awardees
15 October 2018	14 December 2018	2
14 January 2019	15 March 2019	2

The final decision will be given 1 month after the closure date.

Unsuccessful applicants to a call may re-apply to the following call with the same biomarker candidate.

How to apply?

Applicants who fulfill the eligibility criteria and technical requirements (section 2), are invited to contact their regional partner.

The application should be as exhaustive and as accurate as possible. It is possible to select several options if several apply to your biomarker. The use of "not available" or "unknown" will have no negative impact on the evaluation process.

The applicants transmit their application form, including the *de-minimis* self-declaration and any other documentation to their regional partner before the respective closing date (see above).

More information on *de-minimis* regulation is provided at the end of the present guidelines. Once the Biomarker Validation Service has been finalised, the beneficiary SME will receive a notification letter from its regional contact person.

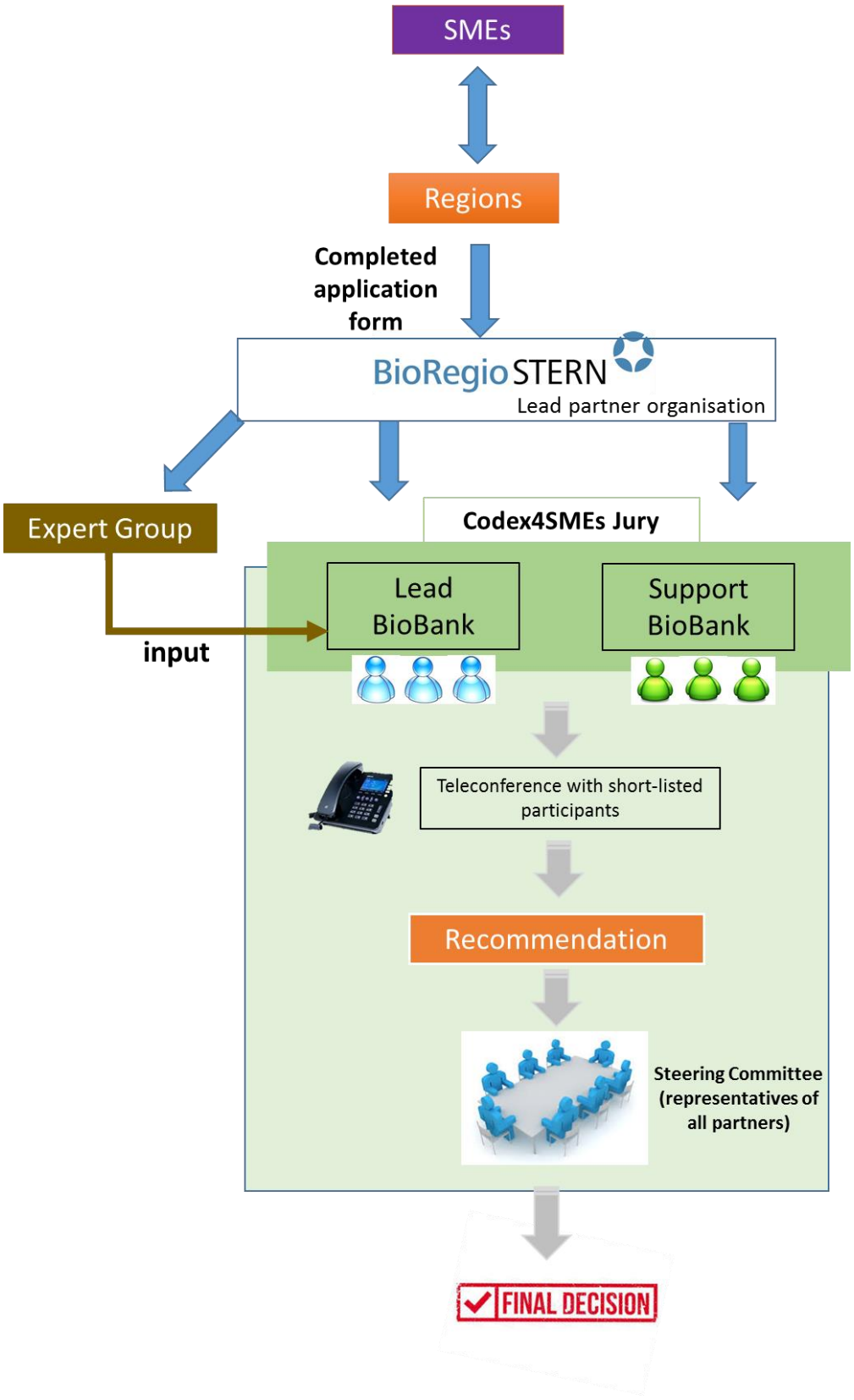
In case the applicants do not have samples available for the Biomarker validation Service to be delivered by the IBBL, the applicants are invited to submit an application for Sample Access by their regional partner.

More information on Sample Access Application are available on the Codex4SMEs website or may be provided by the regional partner.

Applications for Sample Access and for the present Biomarker Validation Service will be evaluated independently from each other.

4. Evaluation

1. An independent group of experts evaluates the applications and gives its input to the Lead Biobank.
2. The two biobanks evaluate the applications according to the evaluation criteria mentioned below.
3. The two biobanks organize a teleconference with the short-listed applicants for a questions and answers session (1 hour maximum).
4. The Codex4SMEs Jury, composed of 3 staff members of each biobank (IBBL and BBG) and of the members of the Steering Committee (representatives of each partner institution of the Codex4SMEs project), selects the winners based on the input given by the group of experts and the evaluation of the two biobanks.
5. The final decision is given one month after the call closure.


SMEs
Regions
Completed application form
BioRegio STERN
Lead partner organisation
Expert Group
input
Codex4SMEs Jury
Lead BioBank
Support BioBank
Teleconference with short-listed participants
Recommendation
Steering Committee (representatives of all partners)
FINAL DECISION

The applications will be assessed based on the following criteria:

1) Scientific excellence and innovation potential
    a. *Soundness of preliminary results/statistical analysis*
    b. *Status of biomarker proof-of-concept – to what extent has the biomarker been verified so far*
    c. *Clinical need for biomarker*
    d. *Commercialisation potential*
    e. *Innovation potential*

2) Technical feasibility
    a. *Assay feasibility*
    b. *Access to biospecimens*
    c. *Is optimisation required?*
    d. *Homebrew or commercial assay*
    e. *Complexity of the biomarker/assay*

Similar weight will be given to scientific excellence and innovation potential, and to technical feasibility.

5. Contact

Regional partners for questions related to application:

- BioRegio STERN, DE
- CURAM, IE
- University of Leicester (and subpartner), UK
- BOM Holding BV, NL
- WestBIC, IE
- Innovation Quarter (and subpartner), NL
- Medicen Paris Region, FR

Point of contact for Biomarker validation related questions:

Monica Marchese, PhD,
Biomarker Validation Scientist

Christelle Bahlawane, PhD
Project manager

E: Codex4smes@ibbl.lu

Additional information on *de-minimis* regulation

1 *De-minimis*[1]

The *de-minimis* rule allows for State aid relevant activities, but only those that are of minimum financial importance, up to a threshold in a rolling three year period, subject to certain administrative steps being taken. The amounts of *de-minimis* aid granted to a single undertaking within the last 3 financial years cannot exceed €200,000[2].

1.1 Single undertaking

Single undertaking means all enterprises having at least one of the following relationships with each other:

(a) one enterprise has a majority of the shareholders' or members' voting rights in another enterprise;
(b) one enterprise has the right to appoint or remove a majority of the members of the administrative, management or supervisory body of another enterprise;
(c) one enterprise has the right to exercise a dominant influence over another enterprise pursuant to a contract entered into with that enterprise or to a provision in its memorandum or articles of association;
(d) one enterprise, which is a shareholder in or member of another enterprise, controls alone, pursuant to an agreement with other shareholders in or members of that enterprise, a majority of shareholders' or members' voting rights in that enterprise.

Enterprises having any of the relationships referred to in points (a) to (d) through one or more other enterprises shall also be considered to be a single undertaking.

Please note that enterprise means here any undertaking performing economic activity.

1.2 Exclusions

De-minimis granted by NWE Programme (both direct and downstream) does not apply to:

(a) aid granted to undertakings active in the fishery and aquaculture sector,
(b) aid granted to undertakings active in the primary production of agricultural products;
(c) aid granted to undertakings active in the sector of processing and marketing of agricultural products, in the following cases:
    i. where the amount of the aid is fixed on the basis of the price or quantity of such products purchased from primary producers or put on the market by the undertakings concerned;
    ii. where the aid is conditional on being partly or entirely passed on to primary producers;
(d) aid to export-related activities towards third countries or Member States, namely aid directly linked to the quantities exported, to the establishment and operation of a distribution network or to other current expenditure linked to the export activity;
(e) aid contingent upon the use of domestic over imported goods.

[1] Commission Regulation (EU) No 1407/2013 of 18 December 2013 on the application of Articles 107 and 108 of the Treaty on the Functioning of the European Union to *de-minimis* aid Text with EEA relevance, http://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1458746162354&uri=CELEX:32013R1407

[2] In the road freight transport sector this threshold is decreased to €100,000 and will not apply for acquisition of road freight transport vehicles.