**DRUG DEVELOPMENT TOOL**
**LETTER OF INTENT**
**DETERMINATION LETTER**
**DDT-BMQ-000165**

November 24, 2025

Pulmonary Fibrosis Foundation
Attention: Peter Schafer & Jennifer Mefford
223 W Jackson Blvd, Suite 350
Chicago, IL 60606

Dear Mr. Schafer and Ms. Mefford:

We have completed our review of the Letter of Intent (LOI) for Drug Development Tool (DDT), DDT-BMQ-000165, received on **April 3, 2025,** by the CDER/CBER Biomarker Qualification Program (BQP), submitted under section 507 of the Federal Food, Drug, and Cosmetic (FD&C) Act.[1]

The LOI is for the PROLIFIC Risk Score (the 4-marker panel of SP-D, CXCL13, TNC, and MMP-7), a prognostic biomarker in patients with Idiopathic Pulmonary Fibrosis (IPF) to be used as a stratification factor or as eligibility criteria in clinical trials to identify patients who are more likely to have clinical events or disease progression (an enrichment tool). The PROLIFIC Risk Score is a composite risk score with specific cut-offs identifying low- and high-risk IPF populations for disease progression.

FDA has made a determination to **accept** the LOI into the CDER Biomarker Qualification Program, contingent upon the adoption of Clinical Consideration #2, below. In preparing to submit a Qualification Plan (QP), address each of the specific considerations and recommendations and any data requests in the body of the QP. In addition, please also provide a summary that cross-references each item listed in the Appendix section of this letter stating where in the submission the responses are located. As this DDT development effort is refined, the submitted data, the specifics of your context of use (including the target patient population), and the design of study(ies) used in the validation of the DDT will ultimately determine which of these considerations and recommendations are most applicable. For more information about your next submission and a QP Content Element outline, please see the BQP Resources web page.[2]

[1] In December 2016, the 21st Century Cures Act added section 507 to the FD&C Act. FDA is now operating its DDT programs under section 507 of the FD&C Act.
[2] Resources for Biomarker Requestors: https://www.fda.gov/drugs/biomarker-qualification-program/resources-biomarker-requestors.

If the program will be submitting clinical data for the purpose of qualification of a DDT, requesters are encouraged to submit clinical data using Clinical Data Interchange Consortium (CDISC) standards to facilitate review and utilization of data. Data sharing and the capability to integrate data across trials can enhance DDT development and utilization. If sponsors plan to use the DDT prior to qualification to support regulatory review for a specific Investigational New Drug (IND), New Drug Application (NDA) or Abbreviated New Drug Application (ANDA) development program, they should prospectively discuss the approach with the appropriate CDER or CBER division.

Please note that section 507 of the FD&C Act includes transparency provisions that apply to your submissions. Certain information contained within your submissions may be made publicly available on the Internet, as required by section 507.[3]

Should you have any questions, please contact the BQP staff at CDER-BiomarkerQualificationProgram@fda.hhs.gov and refer to **DDT-BMQ-000165** in the subject line of your email.

Sincerely,

Vanitha Sekar, PhD
Director, Division of Biomedical Informatics,
Research & Biomarker Development
Office of Drug Evaluation Science
Office of New Drugs
Center for Drug Evaluation and Research

Banu Karimi-Shah, MD
Director, Division of Pulmonology, Allergy and Critical Care
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

[3] Drug Development Tool Qualification Process: Transparency Provisions: https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/drug-development-tool-qualification-process-transparency-provisions.

## APPENDIX

## CONSIDERATIONS AND RECOMMENDATIONS

### Context of Use (COU) Considerations

1. You propose a prognostic COU for the biomarker to inform enrichment of clinical trials in IPF. However, you also state: Changes in PROLIFIC Risk Score may also allow for earlier detection of therapeutic response, while providing insight into mechanism of action of novel therapies, which appears to imply a COU as a monitoring biomarker.
    - Clarify your intended COU. We recommend that you focus on one single COU initially (e.g., prognostic), since the data needed to justify a prognostic COU may differ substantially from the data required to justify a monitoring COU.

### Clinical, Statistical and Analytical Considerations

2. You proposed to use 10% relative decline in percent-predicted FVC as one component of your composite primary endpoint for validation of your prognostic biomarker. We do not consider the relative decline in percent-predicted FVC as clinically relevant or meaningful in the context of a benchmark of clinical decline in IPF. However, we consider the absolute change in percent-predicted FVC clinically meaningful and interpretable in this setting. If you plan to move forward to a qualification plan, you **must use absolute change in percent-predicted FVC** as your benchmark (i.e., the component in your composite endpoint, with absolute change threshold value of 10%) for validation of the prognostic biomarker, otherwise any future submission will not be considered reviewable.
3. You note that serum and EDTA plasma from IPF patients were procured from external biorepositories via Discovery Life Sciences (Huntsville, AL, USA).
    a. Provide the ascertainment criteria utilized to recruit subjects with IPF who provided blood to the external biorepositories (e.g., enrollment criteria or similar, including criteria required for a diagnosis of IPF and summary baseline characteristics).
    b. Clarify whether any of these IPF patients were members of the Pulmonary Fibrosis Foundation Patient Registry, the ISABELA study, or another patient grouping.
    c. If your chosen IPF patient sample represents a subgroup of the full dataset, provide summary information for the full dataset including clinical characteristics, ascertainment, and justification for your subgroup.

4. You note that the PFF Patient Registry Samples (Derivation Set) is characterized as 1222 participants with IPF out of 2003 participants with interstitial lung disease, yet your derivation set contains 657 subjects.
    a. Provide summary disease information (e.g., age range, percent-predicted FVC, use of nintedanib/pirfenidone) comparing the selected derivation set to those not selected for the derivation set.
    b. Provide operating characteristics of the PROLIFIC score for those subjects not selected for your derivation set.
    c. Provide data regarding the number of subjects who provided data to both the PFF Derivation Set and the ISABELA Validation Set, if any.
5. We recommend that you reassess the proposed 4-marker algorithm in light of the revised composite endpoint definition to assure that its performance is maintained. Provide updated analyses in the qualification plan demonstrating the performance characteristics of your proposed biomarker panel using the clinically appropriate endpoint definitions.
6. In your QP, you should address whether including clinical/demographic factors in the calculation of the risk score would improve its performance.
7. The timing of assessment of the biomarkers may be influenced by intrasubject variability. In your QP, you should address factors for optimal timing of sample collection, e.g., do they change during acute illness, seasonally, etc.
8. In the composite endpoint definition, the components of death and lung transplant are direct measures of how patients feel, function or survive while FVC is an indirect measure. In your QP, we recommend conducting a supplementary sensitivity analysis of the performance of PROLIFIC score using a composite endpoint with only the deaths and transplant components, excluding the FVC decline. While this analysis may be underpowered, it could nonetheless provide valuable context for interpreting the clinical significance of the composite endpoint results.
9. Clarify what you mean by this statement from your LOI: Four biomarkers (MMP-7, TNC, SP-D, and CXCL13) were associated with the binary outcome of death, lung transplant, or ≥ 10% relative decline of % predicted FVC, which had a higher event rate due to FVC decline (14.5%), and therefore had the highest overall event rate (total 29.5%) (Figure 1).
10. You note that statistical analyses were performed to define a composite binary outcome of reaching an **estimated** 10% decline in percent-predicted forced vital capacity (FVC), death, or lung transplant in one year. We would normally expect that this composite outcome would be met by actual data/event rates, not based on an estimated decline.
    a. Your use of **estimated** 10% decline in percent-predicted FVC is unclear. Clarify whether the data presented from your derivation and validation sets includes only measured values for FVC at both timepoints (e.g., “time 0” and “time 0 + 1 year”), or whether it also includes estimated values.
        i. FVC decline in IPF is not necessarily linear. Define and justify your method of FVC estimation, if one was used, and clearly state your assumptions regarding linearity, etc.

ii. Similarly, describe the “time 0” timepoint of your percent-predicted FVC and percent-predicted DLCO covariates for each dataset used (e.g., registry entry, trial enrollment, or other)

b. Please confirm percent-predicted FVC refers to patient values compared against population-based reference values (adjusted for demographics like age, height, and sex), and not predictive modeling. Provide the specific reference set used for calculating percent-predicted values. Common standards include the ATS/ERS guidelines (Hankinson et al.) and the Global Lung Function Initiative guidelines (Quanjer et al.) among other established reference sets.

11. You note a threshold value for high versus low risk. While conceptually this may be reasonable, determining a specific cutoff value (i.e., ≥0.34) to be included as part of the biomarker qualification may be outside of the scope of the initial qualification that you propose. Such a cutoff may require additional data validation using a different source. Analyzing the PROLIFIC risk score in the framework of a continuous variable may provide additional statistical power over the binary approach. Please plan to analyze the PROLIFIC risk score in the framework of a continuous variable.
12. As part of your QP, please include a standalone Statistical Analysis Plan (SAP) that describes the statistical methods you intend to use to support qualification of candidate biomarkers. Our preliminary statistical comments can be found below. We may have additional comments on your planned approach when you submit your QP along with the SAP.

    In the SAP, we recommend you include the following key components:

    a. The primary statistical approach to evaluate the PROLIFIC Risk Score performance.
    b. Appropriate adjustments for multiple comparisons, if applicable.
    c. The validation set (ISABELA, N=229) is considerably smaller than the derivation set (N=657), which may limit the power to detect differences in model performance. A formal sample size calculation for validation set should be provided to ensure adequate power.
    d. In addition, provide the selection criteria and rationale for choosing the 229 patients from the total of 1,306 enrolled patients from ISABELA 1 and ISABELA 2, including any exclusion criteria applied and potential selection bias considerations.
    e. Since both ISABELA 1 and 2 were halted following the recommendation from the Independent Data Monitoring Committee, we recommend you explore other options (e.g., successful studies) to form your validation set, if applicable.
    f. Missing data handling procedures and sensitivity analysis to missing data patterns
    g. Subgroup analyses, e.g., age, sex, smoking status, antifibrotic medication use, disease severity at baseline (% predicted FVC, % predicted DLCO), etc., which should be pre-specified in the SAP.

h. Any other pre-specified statistical approaches that are considered appropriate to include in the SAP.

13. The analytical performance studies described below are what are typically provided for validation of biomarker assays. In your qualification package (QP), please provide the following analytical performance data (where applicable) for each of the constituent biomarkers measured by your device that are part of the PROLIFIC Risk Score and as well as the PROLIFIC Risk Score that is the final output of your device. We recommend that you conduct your assessment using samples collected from patients representative of the full intended use population. If you determine that some of the analytical testing described below is not necessary or applicable to your device (or, conversely, if you determine that additional analytical testing is needed), in your QP please clearly explain why this analytical testing is or is not necessary. In your explanation, please include a description of the goals of your study and provide a rationale describing why the analytical performance characteristics you have chosen to evaluate (and the resulting performance) are adequate to support your context of use.
    a. Measuring range of the test system, including:
        i. Limit of Quantitation
        ii. Limit of Detection
        iii. Linearity of the entire measuring range
        iv. Recovery evaluation of the entire measuring range to support the analytical accuracy for each of the proteins included in the biomarker assay
    b. Intra-assay and inter-assay precision. Samples used for these precision studies should span the measuring range of the assay, and these samples should cover any proposed cut-offs and clinical decision points.
    c. Analytical interference testing (based on a risk analysis for potential interfering substances for all analytes), including exogenous and endogenous interference. Samples used for interference testing should include samples that cover any proposed cut-offs and clinical decision points.
    d. Sample collection and storage conditions (such as short- and long-term stability, shipping stability), taking into consideration how long samples were (or will be) stored for all analytical and clinical validation studies.
    e. Sample type matrix comparison comparing the performance of your device in your primary sample matrix (i.e., serum) to any additional matrices you plan to claim by testing native samples from your intended use population across the measuring range of your assay, covering all important cut-offs and clinical decision points. This would only be applicable if you plan to claim other sample matrices in addition to your primary serum sample matrix.
    f. A description and annotation of all samples tested (e.g., spiked, diluted, natural, etc.) for the analytical validation studies, including number of replicates tested, concentration of samples, etc. You should also clearly describe all acceptance criteria and how the performance of your assay is

adequate to support your COU. The analytical performance requirements (i.e., acceptance criteria) should be defined based on the clinical needs of the biomarker (e.g., the total analytical error budget should be low enough so as to not mask clinically meaningful differences).

g. Please describe the quality control and calibrator material that are used by your device.
h. Description and traceability of any standards used for the assay as well as traceability of the assay, controls, and calibrators.
    i. Please describe how you intend to establish traceability for each analyte that your device is intended to measure to ensure your device performance is maintained over time. For example, how will you ensure that the test results are consistent over time and how drift be prevented in the PROLIFIC Risk Score measurements over time? In your QP, please describe the complete traceability of your assay, standards, controls, and calibrators and how/if they are linked to higher order reference materials.

We recommend that you consider the following Clinical and Laboratory Standards Institute (CLSI) guidelines when designing and evaluating your studies.

| **Performance characteristic** | **CLSI guideline** |
|---|---|
| Precision (including but not limited to repeatability, within laboratory, between lots, between instruments, between operators, between sites reproducibility) | CLSI EP05-A3 (Reaffirmed: September 2019) "Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline" - Third Edition |
| Linearity of the analytical measuring interval | CLSI EP06 "Evaluation of the Linearity of Quantitative Measurement Procedures" - 2nd Edition |
| Systematic measurement error (bias or difference) | CLSI EP09c "Measurement Procedure Comparison and Bias Estimation Using Patient Samples" - 3rd Edition |
| Total analytical error (TAE) | CLSI EP21 "Evaluation of Total Analytical Error for Quantitative Medical Laboratory Measurement Procedures" - 2nd Edition |
| Traceability | CLSI EP32-R Metrological Traceability and Its Implementation; A Report |
| Detection capability (Limit of Blank, Limit of Detection, Limit of Quantitation) | EP17-A2 "Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline" - 2nd Edition |
| Interference (endogenous and exogenous substances) | EP07 "Interference Testing in Clinical Chemistry", and EP37 "Supplemental Tables for Interference Testing in Clinical Chemistry" |
| Reference intervals | EP28-A3c "Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory"- 3rd Edition |

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