LETTER OF INTENT
DETERMINATION LETTER

DDTBMQ000101
July 3, 2020

Innovative Medicines Initiative (IMI) TransBioLine
Drug-Induced CNS Injury (DINI) Work Package
Attention: Dr. Lidia D. Mostovy
One Health Plaza
East Hanover, New Jersey, 07936

Dear Dr. Lidia D. Mostovy:

We are issuing this letter to Innovative Medicines Initiative (IMI) TransBioLine Drug-Induced CNS Injury (DINI) Work Package, to notify you of our determination on your proposed qualification project submitted to the Center for Drug Evaluation and Research (CDER) Biomarker Qualification Program (BQP). We have completed our review of your Letter of Intent (LOI) deemed reviewable on March 18, 2020, and have concluded to **Accept** it into the CDER BQP[1]. Based on our review of the LOI, we agree there is an unmet need and therefore support development of the proposed panel of safety biomarkers that may potentially enable detection of acute drug-induced central nervous system (CNS) injury risk in Phase 1 trials.

You have proposed qualification of a panel of five serum biomarkers [glial fibrillary acid protein (GFAP), ubiquitin C-terminal hydrolase L1 (UCH-L1), neurofilament light chain (NFL), phosphorylated neurofilament heavy chain (pNFH), and microtubule associated protein tau (tau)] as safety biomarkers to aid in the detection of acute drug-induced CNS injury risk in Phase 1 trials in healthy volunteers when there is an a priori concern that a drug may cause CNS injury in humans.

Your next stage of submission, a Qualification Plan (QP), should contain details of the analytical validation plan for the biomarker panel measurement method, detailed summaries of existing data that will support the biomarker panel and its context of use (COU), and include descriptions of knowledge gaps with proposed mitigation strategies. If future studies are planned, please include detailed study protocols and the statistical analysis plan for each study as part of your QP submission. Below, we provide you with specific considerations and recommendations to help improve your preparation for, and submission of the QP. For more information about your next submission and a QP Content Element outline, please see the BQP Resources for Biomarker Requestors web page.[2]

[1] In December, 2016, the 21st Century Cures Act added section 507 to the Food, Drug, Cosmetic Act (FD&C Act). FDA is now operating its drug development tools (DDT) programs under section 507 of the FD&C Act.
[2] https://www.fda.gov/drugs/cder-biomarker-qualification-program/resources-biomarker-requestors

As this biomarker development effort is refined in subsequent submissions, the submitted data, the specifics of your context of use (including the target patient population), and the design of study(ies) used in the clinical validation of the biomarker will ultimately determine which of the recommendations below are most applicable. We appreciate the complexity of the proposed endeavor and note its ambitious goals. However, we have several concerns related to the studies proposed by you and interpretability of potential results.

Biomarker Considerations

Requestor's Description: *A panel of 5 biomarkers including:*

Acronym	Name (Unique ID (HUGO ID))
GFAP	Glial fibrillary acid protein (HGNC:4235)
UCH-L1	Ubiquitin C-terminal hydrolase L1 (HGNC:12513)
NFL	Neurofilament light chain (HGNC:7739)
pNFH	Phosphorylated neurofilament heavy chain (HGNC:7737)
Tau	Microtubule associated protein tau (HGNC:6893)

FDA's questions for continued development of the biomarker description:

1. We agree that the biomarkers in your proposed panel of biomarkers have been shown to increase with one or more type of CNS injury. For example, GFAP and UCH-L1 are measured by the Banyan device, which was cleared by the Center for Devices and Radiological Health (CDRH), to aid in the evaluation of patients with suspected traumatic brain injury (TBI). Increased serum NFL and pNFH have been observed in diseases that cause inflammatory injury to the CNS such as multiple sclerosis (MS). Finally, tau protein has been proposed to correlate with progression of Alzheimer's disease (AD) and dementia. Even though we have no issue with any of these biomarkers being proposed as parts of a panel intended to detect CNS injury, we cannot confirm that this particular panel would exclusively provide a safety signaling mechanism capable of detecting every possible CNS injury that might occur in patients. Likewise, while these markers may indicate abnormal CNS conditions, please provide a rationale for why they may indicate drug-induced CNS damage and could serve as an indicator of drug toxicity specific to the CNS.

Context of Use (COU) Considerations

Requestor's COU: *A blood-based safety biomarker or biomarker panel to aid in the detection of acute drug-induced CNS injury risk in Phase 1 trials in healthy volunteers when there is an a priori concern that a drug may cause CNS injury in humans.*

FDA's suggested COU for continued biomarker development: *At the moment, we agree with your suggested COU. Revisions of the COU might be necessary in QP or FQP stage based on the data available. However, several terms in the COU needs to be properly defined.*

2. In your QP submission, please clearly define what "a priori concern" means, and how it impacts the decision to study the novel safety biomarker panel. To better understand the benefits of the identified panel of CNS biomarkers as a Drug Development Tool, and to continue to refine the COU, please provide the following information:

    a. Please clearly define what "acute" means in this context and provide a rationale for this use based upon prior knowledge of drug mechanism of action and latency to neurotoxicity. The mechanisms by which drugs could exert neurotoxicity are diverse, and different parts of the CNS could be involved at different times. The timing of onset, peak effect, and duration of toxicity could, and likely do, differ between the biomarkers in the panel and a given therapy's toxic mechanism. Therefore, defining a reasonable timeline in which your panel would be appropriate to screen for toxicity associated with a given therapy would be an individualized output of the interplay between the timing of the appearance of the marker(s) and the timing of onset of the toxic effect(s) of the therapy being evaluated. Since this panel would be used with therapies for which toxicity is suspected but not evident in prior study, the window of time when changes may be noted in the panel may be indefinite. You should provide a rationale for how various drug-induced injury mechanisms would be taken into account by this proposed biomarker panel.

    b. Please provide further information regarding how results from your proposed study could potentially impact dose selection in human trials, in relation to the no observed adverse effect level (NOAEL) derived from nonclinical studies. We are concerned that if a Phase 1 trial had no signs of CNS toxicity based upon the biomarker screening suggested by this analysis, this may provide false reassurance and result in false negatives regarding CNS toxicity in subsequent trials.

Analytical Considerations

3. Pre-Analytical Considerations (Section 6.1 of the Work Package):

    You proposed to develop and implement a rigorous pre-analytical sample collection, processing, and shipping protocol. Because different biomarkers can be affected differently by pre-analytical variables, we recommend evaluating the impact of these variables on the recovery and quantification accuracy of each biomarker. Additionally, it is necessary to collect and process all samples tested in the proposed analytical (Section 6.2) and clinical validation studies (Section 7) using the same pre-analytical protocol. The information (e.g., time frames for sample collection, process, and shipment) obtained from the proposed pre-analytical studies should be used to define the final test procedure for specimen handling

and processing.

4. Analytical Considerations:

   You proposed to conduct the following analytical performance evaluation studies for the Neurology 4-Plex (NFL, Tau, GFAP & UCH-L1) and Simoa pNF-Heavy Discovery Kit to support the intended clinical use: standard curve performance, intra-run and inter-run precision, assay dynamic range/assay limits (ULOQ, LLOQ), parallelism, reproducibility of endogenous analyte and bench-top, freeze-thaw and long-term stability. We do not believe that the proposed performance evaluation studies are adequate to support the analytical reliability of the assays for the proposed clinical indication. We have listed the additional analytical validation studies that should be performed:

   a. *Interference*: Because false test results can be caused by interfering substances, we recommend evaluating assay interference by endogenous and exogenous interfering substances such as commonly prescribed and over-the-counter medications as well as the drug to be evaluated in the Phase 1 trial. Because the SIMOA immunoassays employ specific biotinylated detection antibodies (please refer to Bioanalytical Methodology section on page 3 of the Method Validation Plan) and because biotin levels higher than the recommended daily allowance may cause interference with lab tests (https://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm586505.htm), the Agency recommends biotin interference testing of up to 3500 ng/ml for new streptavidin-biotin-based assays.

   b. *Analytical specificity:* You should also evaluate analytical specificity to rule out cross-reactivity with other serum proteins present in the specimens.

   c. *High-dose hook effect:* A high dose hook effect study should be performed to demonstrate that there is no suppression of signal that could lead to an underestimation of analyte concentration for a patient with an excessively elevated analyte concentration.

   d. *Reproducibility:* To ensure that all significant sources of assay variability that could contribute significantly to total imprecision during normal operation in the laboratory are adequately addressed, we recommend that you also evaluate lot-to-lot, instrument-to-instrument, and site-to-site variability when applicable. When these variation factors are incorporated, the type of precision study may be best described as a reproducibility study. A site-to-site reproducibility study may not be required if testing is conducted only at a single site.

   e. Because the analytical validation studies are designed to demonstrate the performance of an assay throughout the claimed analytical measuring range, native specimens with analyte concentrations that span the entire measuring range should be tested.

Precision performance of the assays should be demonstrated across the entire measurement range for each biomarker.

f. We highly recommend that the assays be analytically validated by evaluating each performance parameter per the recommended methods, study designs, and applicable data analyses described in Clinical and Laboratory Standards Institute (CLSI) guidelines listed below.

Performance characteristics	CLSI guidance documents
1. Precision (includes repeatability, within-laboratory, lot-to-lot, and instrument-to-instrument 2. Reproducibility (site-to-site)	**CLSI-EP05-A3**: *Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline —Third Edition*
3. Linearity and analytical measuring range (AMR)	**CLSI EP-6A**: *Evaluation of Linearity of Quantitative Measurements: A Statistical Approach*
4. Limit of Blank (LoB), Limit of Detection (LoD) and Limit of Quantitation (LoQ)	**CLSI EP17-A2**: *Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures— Second Edition*
5. Interference	**CLSI EP07-A3**: *Interference Testing in Clinical Chemistry; Approved Guideline—Third Edition*. **CLSI EP37**: *Supplemental Tables for Interference Testing in Clinical Chemistry*

It is important that, for all performance validation studies, the acceptance criteria be pre-specified. The specification of each performance characteristic should be clinically acceptable to ensure that the assays meet the intended use. It was noted, for example in the manufacturer data sheets, that in the spike and recovery study (to assess trueness), the recovery of the biomarkers measured by the Neurology 4-Plex Kit in the spiked serum samples ranges from 52% to 75%, which would not have met the acceptance criteria for accuracy of this assay due to observed deviation from the true value. On the same note, in the Method Validation Plan, the pre-specified acceptance criteria for the intra- and inter-precision studies of ±20% are not sufficiently stringent, as such high imprecision could have impact on the usefulness of these assay results for clinical decisions. We typically recommend a total within-laboratory %CV of ≤10% for devices that employ technology similar to these two assays.

For a combination of the individual biomarker measurements into an algorithm, additional

analytical performance studies are required based on the composite scores of all the biomarkers measured. We suggest that you refer to the "*Class II Special Controls Guidance Document: Ovarian Adnexal Mass Assessment Score Test System*" (available at https://www.fda.gov/media/80370/download) for a discussion of recommendations applicable to tests that measure separately one or more proteins obtained from patient specimens.

5. Analytical Consideration related to Use in Drug Development (Section 7.1 of the Work Package)

   You proposed to measure the five CNS-injury biomarkers in serum collected from NHVs (normal healthy volunteers) treated in Phase 1 trials to determine if their biomarker levels exceed the thresholds associated with increased risk of CNS injury as determined in your proposed development plan. Because the thresholds for TBI biomarkers are defined by the time from injury to blood draw, it is not clear how long after receiving a treatment (e.g., drug, chemotherapy, etc.) the NHVs in a Phase 1 clinical trial will be tested. If you are proposing to perform serial (repeated) measurements of CNS-injury biomarkers in serum samples obtained from NHVs after receiving a treatment to monitor the risk of drug-induced CNS injury, the proposed number of follow-up measurements and the respective timing of these measurements following a treatment should be provided.

6. Comparison of Serum and CSF (Section 7.3.1 of the Work Package)

   The purpose of the proposed study is to determine if blood sampling can replace cerebrospinal fluid (CSF) sampling via lumbar puncture for a particular biomarker. You proposed to determine levels of the five protein biomarkers in paired serum and CSF samples from 30 patients with MS and 30 patients with TBI to analyze the relationship between serum and CSF measurements. It is not clear whether CSF and blood samples will be collected concurrently from patients after a suspected head injury. For a valid comparison, the samples should be collected concurrently. Additionally, to evaluate the correlation between serum and CSF measurements, we recommend that you test at least 40 paired samples from patients with each condition, taking into consideration the desired confidence limits.

7. Establishment of Reference Ranges (Section 7.3.2 of the Work Package)

   You proposed to conduct a reference range study by testing a total of 280 normal healthy controls and analyzing the influence of age, sex and ethnicity on the five biomarkers. It is not clear how you plan to conduct this study and analyze the resultant test data. We recommend following the study design and data analyses described in the CLSI guideline EP28-A3c: *Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline –Third Edition*. It is important the apparently healthy subjects be representative of the U.S. population in terms of age, gender and race to

ensure that the estimated reference value of each biomarker is applicable to this population.

8. Exploratory Phase (Section 7.3.3.1 of the Work Package)

   Traumatic Brain Injury (TBI)

   a. To establish the threshold that is predictive of TBI for each biomarker, you propose to measure the five CNS-injury proteins in serum samples collected within 12 hours of injury from patients *diag*nosed with mild/moderate TBI (Glasgow Coma Scale score of 9-15). It is not clear what clinical criteria and tool(s) will be used to make *a diagnosis of TBI*. It is also not clear why you propose to include subjects with moderate TBI (Glasgow Coma Scale score 9-12) for defining the cutoff thresholds for GFAP and UCH-L1, considering that these biomarkers are currently used to rule out the need for a CT scan among patients with mild TBI (Glasgow Coma Scale score 13-15) presenting at emergency departments in whom a head CT is felt to be clinically indicated. It is important to consider that the threshold established for one specific context of use (e.g., detecting intracranial lesions on head CT scan in patients with suspected traumatic brain injury) may not be optimized for others (e.g., diagnosis of TBI). To ensure that the threshold of each biomarker is defined optimally for its proposed context of use, it is important that you describe in detail the patient population to be included in the proposed study intended to define the thresholds for the two TBI biomarkers.

   Multiple Sclerosis (MS)

   b. To define the cutoff threshold that is predictive of clinically isolated syndrome (CIS)/MS for each biomarker, or combinations of biomarkers, you proposed to measure the five CNS-injury proteins in baseline and one-year follow-up serum samples. Because the levels of biomarkers may increase with disease activity, it is not clear which measurements (baseline or one-year follow-up) will be used to define the threshold of each biomarker. Additionally, because the proposed patient serum samples have been stored for extended periods, we recommend that you evaluate the stability of each biomarker in the archived samples to ensure that the threshold for each biomarker is defined optimally. If samples that have been subjected to more than one freeze/thaw cycle are to be included in defining the threshold, you should determine the effect of repeated freezing and thawing on the levels of the biomarkers in the archived patient samples.

9. Confirmatory Phase (Section 7.3.3.2 of the Work Package)

   Drug-induced CNS injury ("chemobrain")

   a. In the confirmatory phase, you proposed to measure the five CNS-injury proteins in

biospecimens collected from 50 patients before and 5 months after receiving chemotherapy (treatment arm) and from 50 patients in the control arm at baseline and 5 months in the CICARO (Chemotherapy-induced Cognitive Alterations in Recruits with Ovarian and Breast Cancer) study.

b. You proposed to compare the biomarker levels in the patient populations (i.e., patients with histologically confirmed mammary carcinoma or ovarian carcinoma) with reference ranges obtained in healthy controls. Because the aforementioned oncology patients do not represent the proposed intended target population (i.e., the NHV population of Phase 1 clinical trials), it is important that you *(i)* characterize the intra-individual variability of *baseline* measurements in both the treatment and control arms and *(ii)* compare the *baseline* measurements with the reference ranges obtained in healthy controls. It is not clear what you would propose to do if the study data shows that the baseline measurements obtained from the oncology patients are substantially higher than the reference intervals established for the biomarkers (refer to Section 7.3.2) or if patient samples have values that are above the thresholds of the CNS-injury biomarkers defined in the TBI and MS patient populations (refer to Section 7.3.3.1).

c. Understanding the stability of specimens stored for extended periods is important for the interpretation of the study results. To demonstrate that time in storage does not compromise the interpretation of the study findings, we recommend providing information on the storage conditions, storage duration, and data to demonstrate that stability of the archived biospecimens from the patients in the CICARO study has not been impacted during storage.

Clinical Considerations

10. You stated that evidence of drug-induced CNS injury will be confirmed by further testing such as with imaging or neuropsychological assessment. In your QP, please explain how trial/cohort/or dose-related decisions will be made in cases where one or more biomarkers indicate potential injury while the clinical testing or imaging, which may not be as sensitive to change, shows no signs of injury.

11. We have significant, broad concerns relating to the proposed methodology and interpretability of potential results. In general, the tissue-level specificity of these biomarkers is unknown. It is likely that drug-induced neurotoxicity varies in terms of mechanisms of damage, latency of effect, and specific CNS tissues affected. The success of this proposal is contingent upon generalization of results from three populations with important differences in mechanisms of injury, confounding factors, potential reversibility of injury, and timing of injury. At this time, it is difficult to envision a scenario where results from these three diverse populations could be generalized to another patient population

(NHVs with possible drug-induced neurotoxicity) in a meaningful way that adequately captures the mechanism, timing, and clinical relevance of CNS injury in the setting of all possible drugs.

12. The specificity of the proposed biomarkers to the CNS is unclear, and the proposed studies do not permit delineation of central versus peripheral nervous system injury. Several of the biomarkers under consideration could be elevated in peripheral nervous system disease processes (NFL in particular), and there is no known way to delineate origin. The exploratory populations (MS and TBI) are both exclusively CNS-related conditions, but the confirmatory population ("chemobrain") has the potential to introduce significant confounding by peripheral nervous system involvement, as chemotherapy agents are known to cause peripheral nervous system toxicity and some of these biomarkers are not necessarily CNS-specific. Therefore, there are significant concerns regarding pooling these populations.

13. We have several concerns regarding the validity and generalizability of the proposed confirmatory population. First, results from this cohort could be confounded by a patient having CNS involvement of their malignancy. Second, cancer-associated cognitive dysfunction is a poorly understood and multifactorial phenomenon, making it difficult to isolate the CNS toxicity of the drugs of interest. Third, results related to UCH-L1 may be confounded, as UCH-L1 can be expressed by breast cancer cells and ovaries. Fourth, the rationale for the timing of biomarker measurements and clinical assessments in relation to chemotherapy administration is unclear and may vary for different drugs. Finally, repeated administration of chemotherapy should be taken into account for this study design because the toxicity of serial administration of an agent may be additive (with itself or other exposures) or differ between early and late cumulative exposures.

14. Regarding the use of potential CNS injury biomarkers in the multiple sclerosis (MS) population, there are several important considerations that should be taken into account if this population is to be used as an exploratory cohort. MS is a heterogeneous, complex disease with potentially different drivers of potential biomarker changes between patients. For example, NfL concentrations in MS vary depending on MS phenotype (relapsing versus progressive disease), MS treatment exposures, current relapse activity, timing in relation to new lesions on MRI, and comorbidities. We note that your proposed cohort includes patients with CIS or early relapsing-remitting MS, which would reduce confounding by MS phenotype to an extent, but the timing of assessments in relation to clinical and MRI disease activity appears variable and treatment (acute and chronic therapy) may affect the proposed biomarker concentrations. These factors should be considered when generating a statistical analysis plan in this population. Moreover, studies examining conversion from CIS to MS suggest that the disease process may occur over years, and so a 1-year follow-up interval may not be sufficient to capture an accurate assessment of disease activity in this cohort.

15. Please clarify the source of patients for the exploratory TBI population.

16. To ensure comparability of the different proposed populations, it is important that the NHV cohort adequately captures an age range that could be generalizable to relevant populations (e.g., MS, TBI, oncology, other healthy volunteers in future studies).

17. The proposed study protocol appears underdeveloped in its ability to sensitively detect clinically meaningful changes that could validate performance of these biomarkers. Additionally, the protocol does not clearly state how clinical assessments would be incorporated into the validation process, which should be similar across the populations of interest. The utility of neuropsychological testing in this setting would depend upon the domains affected, as well as the timing in relation to drug administration. The latency of clinical symptoms following a neurotoxic drug may be long, so effects may not be immediately apparent, and a study design should account for this possibility. The clinical and paraclinical manifestations of drug-induced CNS toxicity will likely vary depending on the drug's mechanism of action. Other clinical manifestations of CNS toxicity should be formally assessed in this program, specifically seizure, ataxia, psychiatric symptoms (e.g. suicidal ideation), and tremor. The addition of an electroencephalogram (EEG) may be helpful to capture epileptogenic potential of potentially CNS-toxic drugs. Finally, the associations between biomarker levels and clinically apparent neurological impairment should be interpreted with caution if the intention of these biomarker thresholds is to detect CNS injury prior to symptom onset.

18. Please state whether these biomarkers have any history of predicting CNS adverse events that occurred in previous clinical studies. You should consider analyzing blood samples from patients who experienced adverse CNS toxic effects in previous clinical studies using banked samples from these studies' development programs.

Statistical Considerations

In general, this study is still at an early planning stage and the statistical analyses described are largely exploratory. The age, gender, and race of participants were mentioned as co-variate(s) but no details were given in the sample planning and data analysis plan. We have the following preliminary statistical comments:

19. You proposed to include 280 NHVs to establish the reference ranges for the 5 biomarkers. Please clarify if you plan to establish the reference ranges for male and female separately, and, if so, whether you plan to ensure adequate numbers of patients from each gender in the sample. Similarly, if age and race are also important for determining the reference ranges for these 5 biomarkers, you may need to include adequate numbers of patients in each age and race group in the data collection to deduce appropriate reference ranges.

20. You proposed to include 100 patients for each of the 3 diseases: TBI, MS, and cancer from

3 large ongoing observational studies, with data from TBI and MS patients as the exploratory phase and data from the cancer patients as the confirmatory phase. However, the 3 disease indications may have quite different demographics such as age, gender and race. For example, TBI patients tend to be younger mostly male patients, and MS, ovarian, and breast cancer patients tend to be mostly female patients. Please clarify if you plan to incorporate sampling planning when you select patients from the larger studies so that the comparisons of the biomarkers are meaningful between the two phases. We note that you mentioned adjustments for possible confounding by factors such as age, gender, and race in the regression models, but if you do not have large enough sample sizes, there could be serious limitations of the study results even after adjusting for the age, gender, and race in the regression models.

21. In establishing the reference ranges of GFAP, NFL, pNFH, Tau and UCH-L1 serum biomarkers collected from NHVs with no known CNS disease or injury, you planned to use 10 NHVs (10 NHV x 3 longitudinal) to assess intra-individual variability of the five biomarkers and 270 NHVs with single time point. Given the longitudinal nature of drug-induced CNS injury and the need to capture variability by gender and by age group, it is unclear whether only 10 NHVs can properly assess intra-individual variability of the five biomarkers. Additionally, please clarify the timing of collection of the 3 longitudinal biomarker measurements.

22. Regarding the appropriateness of the 5 month-cutoff used in the chemotherapy induced brain injury (“chemobrain”) study, please provide a rationale and justification for this cut-off.

Please address each of the specific considerations and recommendations and any data requests cross-referencing the numbered list above in a separate addendum to your QP submission.

When evaluating biomarkers prospectively in clinical trials, requesters are encouraged to submit study 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 biomarker development and utilization. If sponsors plan to use the biomarker 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.

The BQP encourages collaboration and consolidation of resources to aid biomarker qualification efforts. Any groups (academia, industry, government) that would like to join in this effort or have information or data that may be useful can contact Dr. Lidia D. Mostovy (lidia.mostovy@novartis.com), the point of contact for this project.

Should you have any questions or if you would like a teleconference to clarify the content of this letter, please contact the CDER Biomarker Qualification Program via email at CDER-BiomarkerQualificationProgram@fda.hhs.gov with reference to DDTBMQ000101 in the subject line.

For additional information and guidance on the BQP please see the program's web pages at the link below.[3]

Sincerely,

Christopher L. Leptak -S

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[3] https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/cder-biomarker-qualification-program