NEW YORK STATE | Department of Health | Wadsworth Center

ASSAY APPROVAL FOR TRACE ELEMENTS IN NON-TRADITIONAL MATRICES

Please submit all information as outlined below. Submit one hard copy of the entire package and one electronic copy (as a PDF file on a CD or flash drive) to: **Clinical Laboratory Evaluation Program, Wadsworth Center, New York State Department of Health, P.O. Box 509, Empire State Plaza, Albany, NY 12201-0509; Attn: Assay Validation Review.** Materials submitted, including related data packages, cannot be returned to the laboratory. All materials are maintained under strict confidentiality. As relates to New York State's Freedom of Information Law (commonly called FOIL): The Department's Records Access Officer has advised Wadsworth Center that if documents are marked "proprietary"; "confidential"; or with any labeling indicative of the submitter's desire for an increased level of protection based on the submission content, such protection from immediate release based on a FOIL request is justified. Laboratories will be given an opportunity to block information release if a request for the material is filed under the FOIL, by presenting evidence that the materials contain trade secrets. Marking should minimally appear on the cover page of each unit of material. Documents not marked with such terms will not block release of the submission through a FOIL request.

SECTION 1: GENERAL INFORMATION

Laboratory Name:_____NYS PFI: _____

Contact Person: _____

Phone:_____Fax:_____Contact E-mail: _____

Assay (Test) Name (e.g. selenium measurement): _____

Methodology (e.g., ICP-MS): _____

Analyte(s) included (if different from AssayName): _____

Validated Specimen Type(s) _____

Clinical Purpose: _____

Laboratory Director/Assistant Director (NYS Certificate of Qualification Holder for Trace Elements)

CQ Code_____Signature _____

Laboratory Director (if not the responsible CQ Holder for Trace Elements)

CQ Code_____Signature _____

GUIDANCE FOR TRACE ELEMENT SUBMISSIONS

The guidelines that follow are specific to validate the use of matrices other than whole blood, urine, serum or plasma for trace element testing. Well-defined reference intervals are an essential component of properly validated procedures. Periodically since 1986, we have surveyed the current thinking of leading authorities on whether obstacles to validation of alternate matrices such as hair and packed red cells. Although we have not found the use of alternate matrices to be generally adopted by the medical community, we will consider the use of alternate matrices with the support of well-documented studies that address the following issues:

- Contamination and interfering substances. This is especially noted for hair, which is subject to many pre-analytical variables such as shampoos and dyes. The studies must demonstrate that scissors do not introduce contamination.
- Establishment of clinical validity. Studies need to include a significant number of samples that have been characterized with and without the clinical condition of interest.

Laboratories wishing to offer multi-element hair analysis need to address the issues that have been documented in the literature to date. The consensus among members of the Clinical and Laboratory Standards Institute (document C38-A, 1997), the Centers for Disease Control and Prevention (Dan Paschal, Ph.D., Section Chief, Trace Metals Analysis: Laboratory, technical opinion), and the Mayo Clinic (as published in *Laboratory Medicine,* April, 1999) is that impediments to hair analysis remain; hence, good reference intervals do not exist. The authorities acknowledged the validity of hair analysis for retrospective evaluation of heavy metal exposure, but maintained that hair analysis is essentially of no clinical diagnostic value when considered alone except in the analysis of hair taken from women of childbearing age to determine if there has been recent exposure to methyl mercury from eating contaminated fish.

Excerpts from the documents mentioned above and other references are outlined below:

Y In “Control of Preanalytical Variation in Trace Element Determinations, Approved Guidelines”, NCCLS Vol. 17, No.13. C38-A, September 1997, hair and nail testing are characterized as “of extremely dubious value” due to preanalytical contamination and lack of good reference values. Protocols for collecting hair samples were not provided in this document because of this. In addition, while whole blood collection techniques were described with accompanying reference ranges, there were no references to packed red cells as a legitimate source for laboratory testing.

Y Seidel, et al, published in JAMA, January 3, 2001, vol. 285, no.1, results of hair testing performed in six laboratories using a single hair sample. The conclusion drawn from this study was that hair analysis is generally unreliable. One of the most troubling findings was the inconsistent interpretations of hair element values in evaluating possible health outcomes.

Y On June 12–13, 2001, the Agency for Toxic Substances and Disease Registry (ATSDR) of the federal Division of Health Assessment and Consultation and the Division of Health Education and Promotion convened a panel of experts to discuss the state of the science related to analyzing hair. The group identified factors that limit the interpretation of even the most accurate, reliable, and reproducible laboratory hair test results. Quoting from page six of the summary report, these factors include:

- The lack of reference (or background) ranges in which to frame the interpretation of results. A greater understanding of what is expected to be in hair in the absence of environmental exposures in order to determine whether detected levels are elevated as a result of environmental releases, including possible geographical or regional differences in background levels.
- Difficulties in distinguishing endogenous (internal) from exogenous (external) contamination. Controversy exists concerning the effectiveness of washing hair prior to analysis to eliminate external contamination.
- A lack of understanding of how and to what extent environmental contaminants is incorporated into the hair. Little scientific information is available on the uptake or incorporation of environmental contaminants into hair. Neither kinetic models nor metabolite data are known or fully understood for metals or environmentally relevant organic compounds.
- The lack of correlation between levels in hair and blood and other target tissues, as well as the lack of epidemiologic data linking substance-specific hair levels with adverse health effects. These correlations must be understood before hair analysis results can be used as a diagnostic tool or to predict health endpoints.

Y Concerns in establishing reference ranges were also outlined in the reference "Recommendations of the International Union of Pure and Applied Chemistry Concerning Analytical Quality Criteria in the Biological Monitoring of Toxic Metals" published in the Scandinavian Journal of Work Environment and Health 19:14-18 Suppl.1, 1993. The recommendation of this group was that a complete personal history of the subject would be required to insure clinically applicable reference range for a well-defined group of persons.

Y Scientific skepticism about multi-element hair analysis for patient nutritional assessment as expressed in publications by Taylor (1986), Rivlin (1985), and Barrett (1985).

After careful review of the reviews of reports from expert advisory panels, national consensus bodies and the peer-reviewed literature, it appears that trace element analysis of hair testing for clinical purposes remains highly controversial. There are no studies that hair may serve as a better measure or predictor of disease than other biological samples (e.g., whole blood or urine).

It is the responsibility of a laboratory proposing to offer this testing for patient care to validate its procedures completely with well-defined reference intervals. Should any laboratory design and conduct rigorous investigations to establish valid reference intervals for such analysis, the Department would consider those findings within the context of peer-reviewed literature and the opinions of leading scientific authorities. Please submit validation packages as outlined in these guidelines with completed Section I and Section II to identify where in the package each element can be retrieved.

SECTION 2: COMPLETE THIS PART ONLY FOR THOSE SUBMISSION TYPES LISTED BELOW. ALL OTHER SUBMISSIONS REQUIRE A COMPLETE PACKAGE AS DESCRIBED IN SECTION 3

☐ Research Use Only (RUO) kit or ☐ Investigational Use Only (IUO) kit:
Attach a summary of the establishment of, or verification of, performance characteristics; attach sample patient reports and copy of the package insert.

☐ Addition of an assay under an approved exemption:
Provide the Project ID from your original exemption approval letter, a description of the original exemption, the name of the assay to be added, a summary of the validation performed, and sample reports for all possible outcomes.

☐ Modified FDA or NYS-approved assay
1) Indicate assay modification: ☐Target Population (child or adult):
☐ Purpose of Testing: ☐ diagnostic, ☐ prognostic, ☐ monitoring, ☐predictive

2) Describe how the assay was validated:

☐ Test was validated through comparison to a reference assay. Describe the comparative method and/or identify the reference laboratory

☐Test was validated through correlation of test results to clinical status or condition of test subjects.

SECTION 3: COMPLETE THIS ENTIRE SECTION AND PROVIDE ALL REQUIRED ATTACHMENTS

Please submit the following information, organized as numbered or tabbed attachments as indicated below. If an item is not included, indicate the reason. Indicate the **page numbers and/or tabs where** the items and/or attachments can be found. **SUBMISSIONS THAT ARE NOT ORGANIZED AS DESCRIBED MAY BE RETURNED AND THE REVIEW SIGNIFICANTLY DELAYED.** Please refer to the New York State Specialty Standards of Practice for Trace Elements as noted in this section, when preparing your submission.

Section 3.1: Methods

	Practitioner and patient educational materials that include a description of assay limitations
	Clinical indications for testing, including, where appropriate, the prevalence and description of the medical condition.

	Test subject preparation, specimen collection and handling, specimen rejection criteria, including a description of the mechanism to assure collection and transport requirements have been followed. See Trace Element Standard 2 and 7.
	A description of the assay, assay principle and clinical validity.
	Complete and detailed procedures for performing the assay, including algorithms and flowcharts as necessary and any safety considerations. See New York State Trace Element Standards 8.
	List of equipment / instrumentation essential to the assay.
	Reagents: source, preparation, storage stability and handling.
	Source and verification of standards / calibrators, quality control materials and the type, number, frequency and placement of the QC samples in an analytical run. See New York State Trace Element Standards 5 and 6.
	Calculation of results and interpretation. See New York State Trace Element Standard 9.
	Assay interferences and limitations.

Section 3.2: Requisition And Reporting

	A sample requisition form.
	Sample reports (in the laboratory's official report format) for all applicable findings including interpretive text, assay limitations (both diagnostic and technical limitations) and appropriate patient information.

Section 3.3: References

Page/Tab

	Copies of pertinent literature references that describe the scientific basis and clinical utility of the assay. References must not be based on animal models or epidemiological studies.

Section 3.4: Initial Validation Protocol and Data

Describe the protocols used to validate the assay, including a description of the comparative method and the source and number of specimens. An overall narrative summary of the validation studies performed with results and conclusions must also be submitted. Data to demonstrate the following must be provided (please explain when data is not provided), using an appropriate number of samples across all representative specimen matrices and expected outcomes. Data should be summarized with clearly labeled tables, figures and photographs.

Page/Tab **PRE-ANALYTIC PHASE**

	Analyte and matrix stability.
	Specimen transport conditions.
	Storage time and temperature.
	For hair testing, at least 5 specimens demonstrating the effects of any interferences (endogenous and exogenous).
	Collection of hair samples describing the method used to cut the hair. Studies demonstrating that the method used for cutting does not contaminate the specimen.

Page/Tab	ANALYTIC PHASE
	Accuracy - studies must clearly describe the reference method and/or laboratory used for comparison. Recovery studies may also be performed.
	Precision / reproducibility.
	Reportable range / linearity
	Method detection limit. See New York State Trace Element Standard 1.

Page/Tab	POST-ANALYTIC PHASE
	Data reduction and interpretation.
	Determination of the reference interval. The clinical status of the specimens used as the normal population must be known. It is unacceptable to use samples that have been received in the laboratory for other testing modules.
	Clinical validity, data regarding the degree to which a result or variant predicts a disease or unhealthy state. must be established using specimens from patients with clinical status demonstrating absence of the condition or abnormality being assessed by the assay. Published literature, not including epidemiological studies or animal models, may be used. Complete copies of these references need to be included.
	Where clinical investigations are necessary to determine clinical validity: • Describe the protocols used to determine the clinical status of test subjects. • Describe the procedure used to blind the clinical status of specimens during testing. • Describe the procedures used to resolve discrepant or equivocal test results. • Present data used for the determination of clinical sensitivity, specificity and/or predictive values.

Page/Tab	SPECIMEN RUNS
	Provide actual instrument printouts, worksheets, or charts from a representative run, including all standards and quality control materials. Include information to evaluate quality control.
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Section 3.5: Quality Assurance

Page/Tab	
	Identify the critical steps in the test procedure and the quality control measures taken to control and monitor assay performance for consistent and reliable results.
	Describe the mechanism that will be put in place to verify the accuracy and reliability of test results at least twice yearly for those elements not included in the NYS Proficiency Testing Program, as required in the NYS Quality Assurance Standards.