WAC 296-850-190 Appendix B—Considerations when using the blood beryllium lymphocyte proliferation test in the screening and evaluation of beryllium sensitization—Nonmandatory.

Purpose:

The purpose of this appendix is to provide medical information and recommendations to aid physicians and other licensed health care professionals (PLHCPs) regarding compliance with the medical surveillance provisions of the beryllium standard. Appendix B is for informational and guidance purposes only and none of the statements in Appendix B should be construed as imposing a mandatory requirement on employers that is not otherwise imposed by the beryllium standard (chapter 296-850 WAC, Beryllium). The complete medical surveillance requirements for examinations and procedures under this chapter are described in WAC 296-850-155.

Chronic Beryllium Disease and Beryllium Sensitization:

Chronic beryllium disease (CBD) is a chronic granulomatous (inflammatory) disease primarily of the lung, caused by exposure to beryllium that meets the diagnostic criteria published in the *Department of Labor and Industries Clinical Guideline for the Diagnosis of Beryllium Sensitization and Chronic Beryllium Disease*. Some patients diagnosed with CBD remain free of symptoms following diagnosis, while others develop progressive worsening of clinically significant disease. (Balmes et al. 2014. Page e54) "Medical therapy of CBD is directed at suppressing the immune response to beryllium and subsequent granuloma formation and fibrosis." (Ibid)

Summarizing their review of the development of beryllium sensitization, the Federal Occupational Safety and Health Administration (OSHA) described how the immune systems of sensitized workers have been activated to react to beryllium exposures such that subsequent exposure to beryllium can progress to serious lung disease. (OSHA 2017, page 2492) According to this rule, sensitized workers are considered to be confirmed positive if supported by two abnormal BeLPT test results, an abnormal and a borderline test result, or three borderline test results, or any cases confirmed by the criteria published in the *Department of Labor and Industries Clinical Guideline for the Diagnosis of Beryllium Sensitization and Chronic Beryllium Disease*. It also means the result of a more reliable and accurate test indicating a person has been identified as having beryllium sensitization.

It is prudent to remove sensitized workers from further exposure to beryllium. (Balmes et al. 2014; OSHA 2017)

Additional information regarding beryllium sensitization and chronic beryllium disease are included in the *Department of Labor and Industries Clinical Guideline for the Diagnosis of Beryllium Sensitization and Chronic Beryllium Disease*, which may be requested from the department.

The Beryllium Lymphocyte Proliferation Test:

The beryllium lymphocyte proliferation test is performed by taking lymphocytes from either bronchoalveolar lavage fluid (the BAL BeLPT) or peripheral blood (the blood BeLPT), culturing them *in vitro*, and exposing them to beryllium sulfate to stimulate lymphocyte proliferation. The observation of beryllium-specific proliferation indicates beryllium sensitization.

While test results from either the blood BeLPT or the BAL BeLPT can be used to confirm sensitization to beryllium, (L&I Clinical Beryllium Guideline) it is the blood BeLPT that is typically used when

screening for beryllium sensitization. Abnormal and borderline test results are considered "other than normal" in that they form the basis for diagnosing beryllium sensitization according to the diagnostic criteria used by this rule. Under these diagnostic criteria, no single blood BeLPT result can be used to diagnose beryllium sensitization.

The sensitivity of the BeLPT refers to its ability to correctly yield an other than normal result (i.e., abnormal or borderline) in those who are truly sensitized to beryllium. The specificity of the test refers to its ability to correctly yield a normal result in those who are not sensitized to beryllium.

Per Stange et al. (2004) and Middleton et al. (2006), for a single blood BeLPT the sensitivity is 0.723, and the specificity is 0.9737.

Abnormal or borderline results in workers who are in fact not sensitized to beryllium are considered false positives. Normal results in workers who are truly sensitized to beryllium are considered false negatives.

The diagnostic criteria for confirmed positive beryllium sensitization used by this rule requires any single abnormal or borderline blood BeLPT result be confirmed, which reduces the risk of unsensitized workers being falsely labeled as sensitized by false positive results of the blood BeLPT.

With a sensitivity of 0.723, a single blood BeLPT would be expected to falsely yield a negative result in nearly thirty percent of truly sensitized workers who undergo the test. Testing algorithms have been published that use multiple blood BeLPTs to reduce false negative results while continuing to control the risk of false positives. (Middleton et al. 2006, L&I Clinical Beryllium Guideline)

Thus, by controlling the sequence and number of blood BeLPTs he or she orders, the ordering provider exerts significant control over the risk that workers who are truly sensitized to beryllium could be falsely labeled as unsensitized due to false negative results of the blood BeLPT. The following is designed to provide information to assist the ordering provider who tailors these decisions to the needs of the population and individuals being tested.

These published testing algorithms reduce the risk of false negatives by using split-sample blood beryllium lymphocyte proliferation testing, which is the measurement of blood lymphocyte proliferation in two laboratory tests when a single sample of blood is split into two samples and sent to two independent laboratories, whereupon the lymphocytes are challenged with a soluble beryllium salt and two results returned. (Welch et al. 2004; Middleton et al. 2006; Balmes et al. 2014, OSHA 2017)

The highest sensitivity for performing beryllium sensitization testing using the blood BeLPT (86%) described in NIOSH beryllium rulemaking testimony (NIOSH page 32) relies upon a testing algorithm that requires either one or two rounds of testing, where split-sample blood BeLPTs are performed at each round. Thus, a minimum of two initial blood BeLPTs are obtained from independent laboratories in this testing algorithm, followed if needed by a second simultaneously-obtained pair. (Middleton et al. 2006)

An alternative algorithm with a lower sensitivity (65.7%) uses a single blood BeLPT for the initial round of testing. If the initial result is abnormal or borderline, this triggers a second round of testing with a split-sample blood BeLPT. (Ibid)

Round two split-sample testing:

Although not required by this rule, providers should consider the advantages of using split-sample testing for the second round of blood BeLPT testing, compared to single-sample testing:

• If only a single blood BeLPT is performed during a second round of testing, nearly thirty percent of truly sensitized workers would be expected to have a false negative test result and additional evaluation recommended.

• Split-sample testing for the second round decreases the risk of such false-negative results

• Based on published blood BeLPT performance characteristics (Stange et al. 2004; Middleton et al. 2006) false negative tests are more common than false positives (unless beryllium sensitization is sufficiently rare in the screened population.)

• For some result patterns, split-sample testing may be a faster way to arrive at a sensitization determination, which may be particularly relevant for workers who are receiving medical removal protection benefits while the diagnostic evaluation proceeds

• The risk of false-positives is low with either algorithm that uses split-sample testing (Middleton et al. 2006)

Per WAC 296-850-155 (3)(b)(v) and (vii), employers must make split-sample testing available to workers if requested by the provider who is determining whether an employee is sensitized to beryllium. In addition, WAC 296-850-155 (3)(b)(v) and (vii) requires employers to make multiple rounds of blood BeLPT testing available if requested by the provider. Providers need not cease testing if an initial abnormal or borderline result is followed by single- instead of split-sample testing and a single negative blood BeLPT results, for example.

Per WAC 296-850-155 (5)(c) and (6)(c) providers may at any time choose to refer workers to their choice of either a chronic beryllium disease diagnostic center that is mutually agreed upon by the employer and the employee, or to a facility recognized by the department as a center for research and clinical assessment of chemically related illness (see RCW 51.32.360).

Round one split-sample testing:

Although not required by this rule, providers should also consider circumstances under which split-sample testing at the time of the initial evaluation may be advantageous:

• This achieves the highest sensitivity (86%) of any screening algorithm described in this appendix, while controlling the risk of false-positive test results. (Middleton et al. 2006)

• Except in populations where beryllium sensitization is sufficiently rare, this increase in sensitivity compared to performing the first round of testing with just a single blood BeLPT significantly reduces the number of false negative test results relative to the increase in false positives.

• Patient-specific considerations include the risk of loss-to-follow-up, the expected time to next screening examination, provider index of suspicion, and the consequences of sustaining ongoing exposure to beryllium in the case of a missed diagnosis.

Additional considerations:

The tests used to diagnose beryllium sensitization may have been performed at any time following exposure. (L&I Clinical Beryllium Guideline) Thus, there may be a need to gather additional records of tests that have yielded abnormal or borderline results, but that may not be in the possession of the employer or provided to the provider at the start of the screening examination.

Diagnostic criteria used in the rule anticipate the possibility of false-negative testing: If deemed appropriate, sensitization can be confirmed by bronchoalveolar lavage BeLPT (BAL BeLPT). (L&I Clinical Beryllium Guideline)

Diagnosing chronic beryllium disease using the secondary diagnostic pathway requires all criteria be met and requires the performance of both the blood BeLPT and BAL BeLPT (unless medically contraindicated), but does not require sensitization be confirmed as described in the primary diagnostic pathway. (L&I Clinical Beryllium Guideline)

Concluding recommendations:

Providers should consider providing split-sample blood BeLPTs in nearly all circumstances where round two testing is indicated or required.

Providers should consider whether patient- and population-based considerations warrant using split-sample testing for the first round of blood BeLPT testing.

References:

Balmes, J.R., et al. *An official American Thoracic Society statement: diagnosis and management of beryllium sensitivity and chronic beryllium disease*. Am J Respir Crit Care Med, 2014. **190**(10): p. e34-59.

Beryllium hearing exhibit 005: National Institute for Occupational Safety and Health (NIOSH) Testimony. Docket No. OSHA-H005C-2006-0870-1725.

The Clinical Guideline for the Diagnosis of Beryllium Sensitization and Chronic Beryllium Disease, as published by the Washington State Department of Labor and Industries.

Department of Labor: Occupational Safety and Health Administration (OSHA). *Occupational Exposure to Beryllium*. Federal Register. Vol. 82, No. 5. Monday, January 9, 2017. Rules and Regulations. Docket No. OSHA-H005C-2006-0870.

Middleton, D.C., et al. The BeLPT: algorithms and implications. Am J Ind Med, 2006. **49**(1): p. 36-44.

Stange, A.W., F.J. Furman, and D.E. Hilmas. *The beryllium lymphocyte proliferation test: Relevant issues in beryllium health surveillance*. Am J Ind Med, 2004. 46(5): p. 453-62. Middleton et al. 2006.

Welch, L., et al. *Screening for Beryllium Disease Among Construction Trade Workers at Department of Energy Nuclear Sites*. Am J Ind Med, 2004. 46:207-218.

[Statutory Authority: RCW 49.17.010, 49.17.040, 49.17.050, 49.17.060, and chapter 49.17 RCW. WSR 18-17-156, § 296-850-190, filed 8/21/18, effective 12/12/18.]