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To: ISSC Executive Office
From: J. Michael Hickey, MA DMF, Chief of Shellfish Sanitation and Classification and Susan Boehler, Florence Cenci and Diane Regan, MA DMF, Bacteriologist III
Re: ISSC Request for Interpretation, Date: February 14, 2019
Date: June 18, 2019

Massachusetts Division of Marine Fisheries (MA DMF) would like to comment on the Request for Interpretation received from the ISSC office dated February 14, 2019.

Our review of the interpretation for MO Reference Chapter III, @.01(A) "supporting the NSSP" determined that the MO reference does not address all existing laboratory situations where laboratory support to the NSSP is generated. The interpretation is therefore not complete. The MO reference relies solely on the FDA/State certified Shellfish LEO NSSP technical evaluation to determine laboratory competence and conformance. There are existing laboratory situations however when a FDA/State certified Shellfish LEO NSSP technical evaluation cannot occur. This MO reference therefore must be updated to account for these situations for the benefit of the NSSP and the SSCA. MA DMF has submitted a proposal to the 2019 ISSC conference with a suggested change to this MO reference.

According to the Model Ordinance, a laboratory evaluation conducted by the FDA/State certified Shellfish LEO consists of the following parts:

> MO Chapter I @.03 Evaluation of Shellfish Sanitation Program Elements B.1.
>
> "a. Requirements for evaluation of shellfish laboratories shall include at a minimum:
>
> > i. Records audit of laboratory operations both Quality Systems and Technical methods;
> >
> > ii. Direct observation of current laboratory operating conditions; and
> >
> > iii. Information collection from the Authority and other pertinent sources concerning laboratory operations."

First a desk audit is made of the laboratories Quality Systems.

> MO Chapter 1 @.03 B.1.b.i. Quality System Evaluation. (a).."All nonconformities must be reconciled prior to scheduling an onsite evaluation of technical methods in NSSP laboratories... The Quality Systems evaluation is performed as a desk audit and is in accordance with the checklist found in Section IV Chapter II."

Once the laboratory's Quality System is met with LEO approval, a technical evaluation is conducted onsite using NSSP checklists (MO Section IV. Guidance Documents, Chapter II. Growing Areas, .15 Evaluation of Laboratories by State Shellfish Laboratory Evaluation Officers Including Laboratory Evaluation Checklists). The checklists itemize all technical specifications for the laboratory. The NSSP Laboratory status awarded of Conforms, Provisionally Conforms or Does not Conform is based upon the number and quality of technical violations determined.

The Model Ordinance Chapter 3 @.01C. dictates that a laboratory evaluation will be held at a minimum of every three years as long as the laboratory has satisfactorily passed the initial Quality System Evaluation (QSE). Since no Technical onsite evaluation can occur until the QSE is satisfactorily completed, the time between evaluations could realistically be much longer than 3 years.

> MO Chapter 3 @.01C. FDA Responsibilities. "The FDA will ensure that all laboratories generating data in support of the NSSP will be evaluated at a minimum frequency of once every three (3) years."

For NSSP laboratories that have been in operation, inspected previously and had no significant changes this evaluation processes is viable.

The deficiency of the FDA interpretation for MO Chapter III, @.01(A) is that it requires in all cases that a NSSP technical evaluation be performed before a laboratory provides data to "support the NSSP". A technical evaluation however cannot always occur, nor is it always necessary, nor is it the best avenue for assurance to the NSSP that a laboratory's data is validated and legally defensible.

Examples of laboratory situations that are exceptions are:

1. New laboratories to the NSSP
2. NSSP Conforming laboratories performing new NSSP Methods.
3. Laboratories performing Methods that have no Checklists
4. Laboratories that have completed Single Laboratory Validations
5. Laboratories that conform to other externally accredited programs

<u>1. New Laboratories to the NSSP</u>

A new laboratory must first generate a Quality System Manual and have the Quality Systems Evaluation. The laboratory however cannot write a manual until procedures are in place. Laboratory forms, procedures and protocols must be practiced, streamlined and formalized. Once the manual is approved, then a technical evaluation can occur. However, laboratories must be working and generating data for a technical evaluation to take place. As stated in the MO, records are audited, incubator and autoclave charts are examined; the technical evaluation verifies equipment operation under working conditions. It is the direct observation of laboratory operating conditions. According to this interpretation however, the laboratory cannot generate data or operate until an evaluation has occurred. The laboratory cannot have an evaluation until there is data to examine. It is the chicken or the egg situation.

This similar problem occurred for Depuration Plants. Depuration Plants had to operate and generate data to be evaluated, but they could not technically operate until the verification studies were completed. This developed into the Conditional Protocol Verification phase allowing for Depuration plants to support the NSSP while they were being evaluated. New Laboratories should have the same type of interim operational phase that occurs for a time period before an initial laboratory evaluation to allow for similar NSSP support. The FDA/State certified Shellfish LEO should provide cooperative program validation and method support to the new Laboratory until enough data is generated that a formal evaluation can be held. During this Conditional period of intense review, data generation and split sample verification, data output from the laboratory should be used to support the NSSP.

2. NSSP Conforming laboratories performing new NSSP Methods.

A NSSP conforming laboratory may want to introduce a new approved NSSP method in their laboratory such as: mTec, MSC or MPN-Vp. Conforming NSSP Laboratories have already been evaluated by FDA/State certified Shellfish LEO's and have been found to conform to the QSE and to all technical sections for laboratory equipment and methods currently employed. The only subsections that require evaluation are the ones pertaining to the desired new method. In general, the technical aspects of the laboratory have been found to conform to the NSSP. The only question is the ability of the laboratory to produce compliant data with the new method.

A laboratory evaluation demonstrates that the laboratory is technically correct in both equipment and method procedures but successful conformance to a checklist does not measure that the actual outcome of the data produced in the laboratory will be accurate. The NSSP checklist is a living evaluation document; it is not an accreditation or certification document. It is a partnership document between FDA and the states. The checklist is often used for education and training in the state laboratory.

While an evaluation confirms that a laboratory may be technically conforming, the true test of a laboratory's ability to produce data that is standardized within the NSSP occurs with the evaluation of blind proficiency samples. If the laboratory receives unknown spiked samples and can successfully produce data that statistically conforms to other laboratories, using the same methods, then conformance and standardization is actually verified. A NSSP laboratory technical evaluation only confirms that proper conditions are present in the laboratory to hopefully produce conforming data. It is a technical evaluation of conditions. A successful proficiency completion actually verifies that the laboratory and each analyst in that laboratory does produce conforming data. It is a performance evaluation.

There are two commercial performance based proficiencies available to the NSSP laboratory: FDA CFSAN Shellfish and Water Proficiency Test and the NELEOM Performance Evaluation Study. Performance proficiency can also be shown by completing a successfully transferred Method Verification (Section IV, Chapter II. 20) or with split sampling analysis between several laboratories, with at least one laboratory in conforming status for the method.

A FDA/State certified Shellfish LEO evaluation occurs at a minimum of every three years but may be much longer if the QSE is found to have a deficiency on any unrelated issue. If the SSCA/NSSP laboratory has a need to test it usually is in response to an emerging issue, public health threat and/or classification concern. It is to the betterment of the SSCA and therefore to the NSSP that a response with the new method data starts assessing the concern sooner than the three plus year time frame. If a currently conforming Microbiology laboratory can demonstrate performance proficiency in the new microbiology method with a successful performance evaluation, and the verification of that data produced in that laboratory using the NSSP method is confirmed, then that laboratory should be able to support the NSSP with a "conditionally conforming" status. This support will remain in effect until a FDA/State certified Shellfish LEO possessing three years of bench level technical experience in the method is able to conduct the technical evaluation.

3. Laboratories performing Methods that have no Checklists

There are eleven approved methods in the NSSP that do not have checklists: TC-MF mEndo Agar LES, PSP-RBA, DSP- LC-MS/MS, ASP- HPLC, Vv-EIA, Vv-MPN, Vv-QPCR-MPN, Vp-MPN, Vp-PCR, Vp-Direct Plating Method, and Vc-qPCR. In addition there are 5 approved limited use screening methods for Marine Biotoxin Testing that do not have checklists.

Most of these non checklist approved methods are for Post Harvest Processing for Vibrios or Marine Biotoxins. For Total Coliform or Vibrio testing, a performance evaluation proficiency test exists: the FDA CFSAN Shellfish and Water Proficiency Test. If a laboratory successfully passes a performance proficiency, should the lack of the existence of a technical checklist stop a NSSP laboratory from supporting the NSSP? Of course not. MA DMF in 1991 completed a performance based SLV for MF mEndo Agar LES. For many years this method was listed in the MO Approved NSSP Test Chart A-10 allowing for its use at MA DMF Newburyport as a regulatory method. Performance proficiency at MA DMF Newburyport is verified yearly by participation in the FDA CFSAN Shellfish and Water Proficiency Test using MF mEndo Agar LES by all analysts in this laboratory. In 2014 a draft checklist of this method was jointly created between FDA and MA DMF. This checklist was recently edited by MA DMF and was submitted as a proposal at the 2019 ISSC conference to assist the NSSP in the method's use. If a laboratory has proven its ability by completing a successful performance evaluation for a method then the laboratory should be awarded "conditionally conforming" status and continue to support the NSSP with data from that method.

4. Laboratories that have completed Single Laboratory Validations (SLV)

Any new laboratory method for consideration in the NSSP must submit a SLV to the ISSC Laboratory Committee. The ISSC Laboratory Committee reviews the extensive SLV critique of method data and if found suitable the package is submitted to the conference for adoption as a NSSP method. Eight SLV submissions have become NSSP Methods and are now listed in the current MO Section IV Guidance Documents – Chapter II. Growing Areas, .14 Approved NSSP Laboratory Tests. Laboratories that completed SLV's with the dates completed are the Laboratories of: Dr. Anita Wright 2009 , Dr. Fran Van Dohl, NOAA 2013; Dr. Jon Deeds FDA 2017; FDA Dauphin Island 2015; Abraxis LLC 2009; Jellett Rapid Testing Ltd, 2005; Neogen Corp, 2013 and Marbionc Dev. Group LLC 2017. The submission of data in a Single Laboratory Validation for the potential adoption of a new NSSP method clearly supports the NSSP. Were these laboratories in the status of NSSP Conforming or Provisionally Conforming at this time of their SLV submission? A SLV is a method performance evaluation performed at a laboratory. Once a method performance is validated, the method's technical aspects are determined with the drafting of a required technical checklist. Under the current FDA interpretation, an SLV with accompanying technical checklist could be accepted as an approved NSSP method by the conference, yet the submitting laboratory would not be able to "support the NSSP" with data from their own method. The FDA interpretation indicates that a FDA Shellfish LEO, who is unfamiliar with the technical or performance of the method, (it could not be a FDA certified State LEO since they do not have three years of bench experience with the SLV method) would have to conduct a technical evaluation at the SLV's laboratory using the SLV laboratory's own devised checklist in order for that lab to be "conforming" and able to start generating data in "support of the NSSP". This is not logical. If a laboratory has proven its ability to perform a method successfully with statistically validated, legally defensive data, then the laboratory should be awarded "conditionally conforming" status to support the NSSP with data.

5. Laboratories that conform to other external accredited programs

The NSSP checklists recognize and contain references to other certified laboratory programs such as the US FDA Milk Program, US EPA drinking water/wastewater and accreditation programs such as ISO and AOAC. Laboratories that conform to these other program certification and accreditation standards are required to submit to annual proficiency sampling for their accredited program's standardization. The data from these laboratories therefore has been validated and found compliant for their program use. If the SSCA is using validated data supplied by an external accredited/certified laboratory for the dual purpose of the protection of shellfish resources and public health, the NSSP should continue to recognize and acknowledge the external accreditation/certification process required of these other programs that

the NSSP itself has referenced. Laboratories with these accreditations and certifications have usually complemented or exceeded the requirements of the evaluation process of the NSSP and should be awarded "conditionally conforming" status to support the NSSP.

The FDA/State certified Shellfish LEO evaluation is an important component of the laboratory evaluation process but it is not the only component. Technical competence must be combined with performance competence for the true standardization of laboratories and output data within the NSSP laboratory. Words without action do not verify results.

As a simple analogy: a technical evaluation results in two states A and B having technically conforming cars. Both have engines, horns, lights, tires, seats; they are technically equal and conform to the same standards. But what if state A car was driven by a race car driver and state B was driven by a 5 year old? What if the state A car was a Jaguar and the state B car was a Honda? Technically they are both cars, but would they drive the same? Would they cross the finish line similarly ending at the same spot? The NSSP should want to know that all labs and all analysts driving conforming cars are crossing the finish line at the same spot. Is the count of 14 FC/100ml from NSSP state A lab the same as a count of 14 FC/100ml from NSSP state B lab? The labs are technically the same (conforming) but with the two different drivers the outcomes could be very different. If both labs are able to produce validated counts of 14 FC/100ml, (8 times in a row, no less) in the absence of a technical evaluation, the implication can be made that the laboratory is operating technically correct with no detrimental conditions that are impacting results since compliant data was produced. If a lab is not able to validate counts within a proficiency this should prompt a NSSP technical evaluation to determine what technical conditions are occurring which are detrimental to the laboratory's results.

Completion of a technical evaluation validates and standardizes equipment and technical specifications in the NSSP laboratory but only implies that laboratory performance may produce conforming data. Technical evaluations occur every 3-5 years. Successful completion of a performance evaluation validates and confirms the standardization of data in the NSSP laboratory and implies technical conformance. Performance evaluations occur yearly allowing for better surveillance. The ability of a laboratory to produce statistically confirmed standardized data is the primary goal of the NSSP, not just to be technically correct. Technical evaluations are subject to human interpretation as LEO's must account for differing conditions and equipment. Performance evaluations rely on statistics. The completion of a performance evaluation provides greater assurance than the technical evaluation and is therefore a stronger legally defensible procedure and document. An additional laboratory category of "conditionally conforming" should be included in the MO to allow for laboratories that have completed a performance evaluation to support the NSSP with validated data.

The primary goal of the NSSP, FDA and the SSCA is to assure that laboratories are producing verified and accurate data. The technical evaluation assures that conditions are present in that laboratory for successful data to be produced; it is proactive. It does not however assure that the production of successful data actually occurs nor can the technical evaluation be used for all laboratory situations which support the NSSP. The MA DMF response has outlined 5 instances where technical evaluations cannot occur but where laboratories are able to contribute validated, legally defensible data "supporting" the SSCA and the NSSP; with the cooperative goal of promoting the best interests of the shellfish industry and public health.

MA DMF appreciates the opportunity to comment. MA DMF is available for further discussion and questions.

Attachment: MA DMF 2019 Proposal submission "Conditionally Conforming Laboratory Status"