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21 October 2011

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RE: Regulatory Discussion Minutes from 2011 IMD Consortium Meeting

Dr. Bryan Riley:

BioVigilant would like to thank you for your participation in the recent IMD Consortium Meeting held in Bethesda. Your guidance on validation of RMMs is invaluable to our customers, providing the needed assurance that their validation efforts coincide with FDA expectations.

Below is a summary of the minutes, separated by topic, from the Regulatory Roundtable segment of the IMD Consortium meeting held on October 16, 2011.

Side by Side Testing

1) Would it be acceptable to conduct side by side testing with the traditional method (air samplers) and IMD-A knowing that you will see higher viable/biologic counts on the IMD-A system as compared to the air samplers? Correlation may be decent but not perfect, yet this type of evaluation could be viewed as worst case since the new method is yielding higher counts, correct?

   Answer: Yes, this would be an acceptable approach to take. A similar approach would be applied if another, more sensitive traditional method (air sampler) was evaluated for replacement. The goal would be to show that the method you wish to implement is equivalent or more sensitive than the old method.

2) In which cleanroom classifications should side by side testing be conducted for validation of the IMD-A system?

   Answer: In the areas you will eventually be using the system. In Grade A, it may be more difficult to compare data (zeros compared to zeros doesn't really tell you anything). FDA would like to see data in less controlled environments as well.

3) Would a new IOQ need to be performed before testing in each cleanroom environment if the IMD-A is moved from room to room?

   Answer: No, there is no need to do an IOQ in each environment for collecting data.

4) Does FDA have guidance on the number of samples that should be taken to show "equivalence or better than" when performing side by side testing of the IMD-A system and air sampler(s)? Would FDA statisticians be available to review suggested approaches?

   Answer: We do not have specific guidance on the statistical approach to use. FDA is open to reviewing any approach that is shared. The frequency at which you collect samples with your traditional method should be considered when determining the number of samples needed for validating the IMD-A. If needed, FDA statisticians may be able to review and provide feedback to statistical methods proposed.

Specificity Testing (USP <1223> testing to "encourage false positive results")

1) What does FDA expect in terms of Specificity testing in customer environments?

   Answer: Testing should be conducted in customer environments using your materials and equipment to assess what may be sources of interferents. If, for example, you observe a high false positive rate because of a certain process, e.g., powder fill, then you may not wish to use the IMD-A system in that test location.

2) How should VBNC and dead microbes be approached in customer validation studies considering the fact that VBNC and dead microbes would be detected by the IMD-A and not by traditional methods?

   Answer: You are not expected to validate for VBNC. However, you should look at the potential for false positives in your environment.

3) If false positives are present, would they be held against us?

   Answer: No, but they should be mitigated as much as possible.

Changing EM Limits

1) How does FDA feel about the potential need to change EM limits if the IMD-A system does get higher counts than traditionally seen in each environment?

Answer: There can be differences in the numbers you will see with two different methods. You are somewhat comparing apples and oranges. Limits can change; they just need to be justified. Setting of limits should be meaningful and based on the threat to the product. A risk-based analysis/approach is needed.

A value of the IMD-A system is that it can do continuous monitoring and trending. When doing continuous EM in Grade A, you will see an occasional hit. FDA would be surprised if you don't see one every now and then even though, historically, you may not have seen any with the traditional method. Trending is a reasonable approach to consider when setting new limits.

2) What steps do we need to take to change action and alert limits?

Answer: You can change limits whenever you like. You need to collect your data and perform a risk assessment. We then suggest that you call a meeting with Bryan Riley and regional FDA representatives to review your data. Local inspectors can also be included in this meeting.

3) Would the FDA accept higher action and alert limits for biologics in Grade A than 1 bio count, for example 3 or 10?

Answer: Yes, if this was supported by the data from your validation. It's important to monitor the trends in your environment.

4) In addition to potentially having higher action and alert limits, continuous monitoring increases the likelihood of reaching these limits because of the increased frequency of monitoring as compared to current methods. Would the FDA accept this higher "frequency of failure"?

Answer: Yes, It's important to establish what normal trends in your environments are during validation and monitor for changes in these trends once in use.

Identification

1) What is FDA's position on identification if the RMM cannot collect and identify the microbe it detected?

Answer: The IMD-A system is not capable of identification, but the FDA does see value in continuous monitoring. Contingency plans may be developed and written in your procedure to account for situations where hits are observed on a more frequent basis. A

traditional method may be brought in at that point in an attempt to collect and identify the microbe(s); however, it is quite possible that nothing is captured on the culture plate.

Implementation

1) What is required for FDA to approve the IMD-A?

   Answer: FDA does not approve the EM method nor the EM limit. Review of IMD-A validation and implementation information would be done at inspection. You can involve local inspectors and individuals from FDA headquarters (e.g., reviewers and compliance officers) together before inspection occurs. During the first inspection upon implementation of the IMD-A, it is suggested that reviewers and compliance officers from FDA headquarters appear at your facility alongside the inspectors.

2) If an EM method or EM limit is called out in a prior NDA, DMF, etc. submission with FDA, is it necessary to formally notify FDA of the change in method and/or limit in an annual report for example?

   Answer: No, a formal submission is not necessary even if the method and/or limit was specifically mentioned in a prior submission. Review of IMD-A validation and use is performed when inspection occurs.

3) Would FDA allow replacement of a particle counter with the IMD-A 350 system if strong correlation is continuously demonstrated, even though the absolute numbers are different?

   Answer: That is something FDA has not thought about yet, but we would be willing to consider it.

4) Would it be acceptable to implement the lower flow rate system (IMD-A 300) at 1.15LPM if operating continuously?

   Answer: Yes that would be acceptable. It may take longer to collect the sample volume you desire; however, because it is operating continuously, you will get a better understanding of what is happening in the environment throughout the manufacturing process.

FDA Activities

1) With FDA joining PIC/S, will there be changes in FDA policies regarding RMMs?

   Answer: I am not sure at this point in time. It could be possible.

Sincerely,

Carrene Plummer

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