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Title

A Discussion on Bio-fluorescent Particle Counters: Summary of the Process and Environmental Monitoring Methods Working Group Meeting with the FDA Emerging Technology Team

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Abstract

The Process and Environmental Monitoring Methods Working Group, composed of members from industry and instrument manufacturers, met with the FDA Emerging Technology Team to discuss bio-fluorescent particle counting technology, a type of rapid microbiological method. This is a summary of the meeting including submitted questions and answers, and the Process and Environmental Monitoring Methods Working Group's understanding of the FDA Emerging Technology Team's points made.

Keywords

Bio-fluorescent particle counting (BFPC), rapid microbiological method (RMM), FDA Emerging Technology Team (ETT), environmental monitoring, auto-fluorescence unit (AFU)

Introduction

The Process and Environmental Monitoring Methods (PEMM) Working Group met with the FDA Emerging Technology Team (ETT) on May 18, 2020 to brief them on Bio-fluorescent Particle Counting (BFPC) technology. This manuscript summarizes the questions asked by the PEMM Working Group and responses provided by the FDA ETT. As mentioned on the FDA.gov website, “CDER’s Office of Pharmaceutical Quality created the Emerging Technology Program to promote the adoption of innovative approaches to pharmaceutical product design and manufacturing. Through the program, industry representatives can meet with ETT members to discuss, identify, and resolve potential technical and regulatory issues regarding the development and implementation of novel technologies” (1). The PEMM Working Group is composed of members from the pharmaceutical and personal care industries, BFPC instrument manufacturers, and industry consultants whose aim is to support the adoption of and education on real-time BFPC methods for air and water applications.

BFPC Background

BFPC instruments are a type of rapid microbiological method (RMM), and more specifically, a form of enhanced particle counter capable of the continuous and real-time detection of microorganisms in air and water (2). BFPCs detect microorganisms using a different method of detection than the current culture-based methods employed today. Instead of waiting for sufficient growth so that a colony forming unit (CFU) can be detected, these systems utilize the detection of scattered light for particle enumeration, and intrinsic fluorescence detection for the classification of detected particles as bio-fluorescent particles (BFP, i.e. biologic) or inert (i.e. non-biologic). A BFPC biologic count is often referred to as an auto-fluorescence unit or AFU. These systems are utilized in the environmental monitoring of bacteria and fungi in air in clean

rooms, isolators and manufacturing areas; and in monitoring of bacteria and fungi in purified water and water for injection.

BFPCs provide a fundamentally different and innovative method of microbial detection in air and water, as compared to traditional growth-based methods. With detection based on biologic fluorescence, BFPCs require no sample preparation and are capable of the detection of viable but non-culturable (VBNC) microorganisms since detection is not dependent upon growth.

Furthermore, these systems provide continuous, as opposed to episodic, monitoring of total and BFP counts in air or water and often higher sensitivity than traditional methods. This continuous bioburden monitoring, trending data, and feedback enable real-time assessment and verification of process state; and can be used to improve overall process understanding and process control.

BFPC systems for air and water have been used successfully in non-good manufacturing practice (non-GMP) monitoring applications by a number of pharmaceutical companies. Some of these applications or use cases have recently been presented in journal articles and webinars (3-11).

BFPC have not yet been broadly adopted for GMP applications despite the benefits described above.

Meeting Objectives

The PEMM Working Group met with the ETT to provide an overview of BFPC technology and its current use within industry, and explore how the group could work together with the ETT to support the adoption of BFPCs in the future. The PEMM Working Group expressed a need for guidance from the FDA to facilitate the evaluation, validation and deployment of BFPC systems for GMP and non-GMP applications. The PEMM Working Group asked questions about eight technical and regulatory challenges relevant to implementation of BFPCs, the use of a research exemption by users who wish to assess the technology, and ways in which the Group could

provide information to the inspectorate.

The PEMM Working Group provided the FDA ETT with a summary of the May 18th meeting that included the PEMM Working Group's understanding of the FDA ETT points made during the meeting discussion. The FDA ETT responded that the agency concurs with the PEMM Working Group's understanding. The following bullets highlight the PEMM Working Group's understanding of the FDA ETT points made during the meeting. The FDA ETT reviewed the points below and confirmed that these points are a fair representation of what was discussed at the meeting.

- If using the BFPC system as a process monitoring or control tool in addition to the traditional method, and not as a replacement, there is flexibility in how equivalence of the BFPC technology to the traditional method is shown.
- If the BFPC technology is used as a replacement for the traditional method, it is required to demonstrate that the BFPC technology is equivalent with or superior to the methods currently in use.
- A risk assessment should be performed to understand how the BFPC technology and traditional methods should be used and when the traditional method should be used to attempt to identify an action event on the BFPC system.
- The intended use of the BFPC system will influence the level of side-by-side testing required. If used as a process control tool in ISO 5 environments, then it is recommended to perform side-by-side sampling with both the BFPC technology and traditional method.
- In less critical, ancillary environments, periodic identification may be acceptable and, ultimately, reduced use of the traditional method may be undertaken.

- This technology can improve control when combined with current method. It is recommended to provide more data from the production environment to gain an understanding of the BFPC data obtained and new limits that may be required. During this data collection period, safe harbor may apply and a research exemption may be used.

Submitted Questions and Responses

The specific PEMM Working Group's questions and FDA ETT's responses are listed below. Note that the responses provided by the FDA ETT to the PEMM Working Group's questions regarding BFPC should not be construed as an endorsement of a technology or analytical instrument.

PEMM WG Question: *Does the Agency concur that USP<1223> is the appropriate guidance for demonstrating that BFPCs are suitable for their intended use?*

FDA ETT Response: The Agency concurs that USP<1223> is an appropriate guidance for demonstrating that BFPCs are suitable for their intended use. The Agency also advises careful consideration of the intended use of the method when designing the validation studies and interpreting the results.

PEMM WG Question: *There are concerns about acceptance of BFPCs due to the fact that BFPCs read out in different (and not directly correlated) units as compared to traditional methods. The concern manifests itself as companies' internal concerns that agencies might not approve BFPC technologies. Does the Agency agree that alternative methods, even if not directly correlated to the traditional methods could, with the proper statistical justification, be acceptable as an alternative method?*

FDA ETT Response: Yes, the Agency agrees that BFPCs and traditional methods that

provide results in units that may not directly correlate could be acceptable as an alternative method. Our concern is ensuring that the intended use of BFPCs is well-defined in the environmental control program, and it ensures microbial control that is at least equal to the methods currently in use.

PEMM WG Question: *BFPCs detect more objects than those enumerated by classical plate count methods, among these are viable but non-culturable microorganisms, and some particles such as dead microorganisms and particles that fluoresce at similar wavelengths as bacteria. These objects can be present in air and water streams but heretofore have not been detected by classical plate count methods. Since reliable and precise spiking of microorganisms in air is especially difficult, would an acceptable approach be to trend the BFPC signal to classical air samplers side-by-side (same room but not the same location) to retrospectively demonstrate the co-trending of AFU and CFU counts and activities in the room to validate according to USP<1223>? Would the same trending approach to establish co-trending of AFUs and CFUs also be acceptable for water system validation via USP <1223>?*

FDA ETT Response: The Agency acknowledges the difficulties of precisely and reproducibly spiking air with microorganisms, as well as the value of such studies. We also understand the limitations of methods in discriminating between live and dead microbes, and the potential for data anomalies that can potentially affect analytical reliability. The use of side by side testing to demonstrate co-trending of AFU and CFU would be acceptable as part of validation of BFPCs. The same approach would be acceptable for water testing. However, results from spiking studies of both air and water should be provided to demonstrate specificity.

PEMM WG Question: *We propose that demonstration of control via statistical process control methods is a suitable means for demonstrating continued control. Does the Agency concur that Statistical Process Control can be adequate to demonstrate continued control of an air or water stream?*

FDA ETT Response: Statistical Process Control approaches could be leveraged to demonstrate continued microbial control of air or water from a trending perspective. The Agency would be interested in learning more details about how you would utilize SPC with BFPCs.

PEMM WG Question: *The risk from the Statistical Process control approach is the potential that an inspector, realizing that the process control is over the combined number of particles, might ask for identification or characterization of each AFU. We believe that an initial characterization study of the particles making up the combined AFU count could be used, as long as there are no significant long-term baseline shifts, to provide evidence (coupled with a risk evaluation) that the total AFU count components are understood. Does this Agency concur with this strategy?*

FDA ETT Response: The Agency suggests re-characterization of the particles making up the combined AFU count on a periodic basis as well as after significant changes to the space being monitored. A risk assessment could be used to establish the re-characterization schedule and specific instigating events. The significance of a change in the population should also be assessed.

PEMM WG Question: *There are concerns that not all agencies will approve BFPCs, thereby resulting in delays or supply disruptions. Does this Agency concur that a properly validated, justified and implemented BFPC monitoring device could potentially be used in*

place of traditional monitoring methods?

FDA ETT Response: Yes, this technology provides data on a key microbial count parameter of the classified environment. However, the Agency also continues to expect employment of methods capable of allowing identification of collected microbes (either traditional growth-based methods or alternate methods) in classified environments based on risk assessment, including factors such as criticality of the clean area.

PEMM WG Question: *Lack of clear guidance as to how or where to file use of BFPC technology. We would propose that since these technologies are used primarily for environmental monitoring of facilities, that the appropriate place to file the use of these technologies would be in the Site Master File (SMF). This would allay fears that individual inspectors, who may be less familiar with the technology, will feel compelled to do a complete re-review of the technology at each inspection. If the technology is officially listed on filed documentation, it should be less of concern. Does the Agency agree with the approach of filing BFPC technology in the Site Master File? If not, what filing approach is deemed appropriate?*

FDA ETT Response: The Agency agrees that firms can file BFPC in a Site Master File but does not agree that this is the most effective approach to allay the potential concern of an investigator being unfamiliar with this technology (see Additional Comments from the Agency - below).

PEMM WG Question: *Implementation of these technologies into existing facilities can provide significant benefits. The perceived risk, however, is that changes to a licensed product or facility engender risk to continued production. As proposed in question 7, we would propose that the use of BFPC systems be included in a Site Master File. Does the*

Agency agree that introduction of BFPCs into existing Site Master Files could be performed as an annual update of a Site Master File? Would such an SMF update necessitate a BLA/NDA update or notification if those filings are otherwise silent on the environmental monitoring methods?

FDA ETT Response: See Additional Comments from the Agency (below)

FDA ETT Additional Comments from the Agency: BFPC utilization at a facility can be submitted to a Site Master File. However, submitting this information to a SMF is not sufficient to ensure that the Center facility assessors and field investigators are suitably knowledgeable about this technology.

PEMM WG Question: *The PEMM group would like to understand if, under the PAT initiative, a research exemption applies to BFPC users as they explore ways to better control their processes, as long as validated, traditional methods are still used?*

FDA ETT Response: The Agency typically would not assess data collected from an alternate analytical method during an inspection if currently acceptable, validated methods are being used to control the process. We refer to the following paragraphs from the Guidance for Industry PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance, September 2004. (Some segments underlined for emphasis).

“In the course of implementing the PAT framework, manufacturers may want to evaluate the suitability of a PAT tool on experimental and/or production equipment and processes. For example, when evaluating experimental on- or in-line process analyzers during production, it is recommended that risk analysis of the impact on product quality be

conducted before installation. This can be accomplished within the facility's quality system without prior notification to the Agency. Data collected using an experimental tool should be considered research data. If research is conducted in a production facility, it should be under the facility's own quality system.

When using new measurement tools, such as on- or in-line process analyzers, certain data trends, intrinsic to a currently acceptable process, may be observed. Manufacturers should scientifically evaluate these data to determine how or if such trends affect quality and implementation of PAT tools. FDA does not intend to inspect research data collected on an existing product for the purpose of evaluating the suitability of an experimental process analyzer or other PAT tool. FDA's routine inspection of a firm's manufacturing process that incorporates a PAT tool for research purposes will be based on current regulatory standards (e.g., test results from currently approved or acceptable regulatory methods). Any FDA decision to inspect research data would be based on exceptional situations similar to those outlined in Compliance Policy Guide Sec. 130.300. Those data used to support validation or regulatory submissions will be subject to inspection in the usual manner.”

PEMM WG Question: *We are also very interested in learning how we may provide more information on this technology to inspectorate.*

FDA ETT Response: The Agency would appreciate the PEMM Working Group's sharing information and materials with FDA that could be used as part of our internal training on BFPC. Examples include publications, validation studies and slides describing the technology.

Conclusion

The PEMM Working Group requested the opportunity to continue communication with the ETT. The ETT was receptive to this request and has provided points of contact for future communication. The topics highlighted for future discussion include: validation of BFPC technology; use of statistical process control, including PEMM provided examples; inspectorate training and PEMM provided information on BFPC technology; and how the use of BFPC technology for water monitoring may be different than for air monitoring.

Conflict of Interest Declaration

The PEMM Working Group includes vendor, end user and consultant members. Each author's affiliation is provided in the list of authors.

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