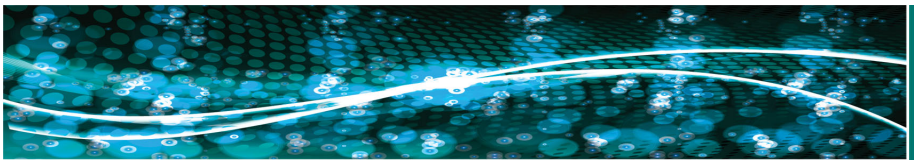

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Testing Recommendations for Online Water Bioburden Analyzer Implementation

Introduction

Bio-fluorescent particle counters (BFPC) for water, also referred to as Online Water Bioburden Analyzers (OWBA), support a number of applications in pharmaceutical water bioburden monitoring. The advantage of these systems is that they deliver real-time and continuous sampling. Their applications range from ***non-GMP*** use as process monitoring and control tools to ***GMP*** applications where conventional testing is reduced. When used as a processing monitoring and control tool, traditional monitoring of the water system remains in place and the OWBA system serves as a complementary tool. In such applications, the extent of testing required before OWBA implementation may not be as great as compared to the validation testing needed for GMP applications like those targeting a reduction in traditional monitoring. This document describes steps and testing considerations to support OWBA implementation. The approaches can vary depending on intended use of the system.

High-level Comparison

BioVigilant offers three document templates to support qualification of the IMD-W™ OWBA. These documents include an Installation and Operation Qualification (IOQ), Performance Qualification (PQ), and Method Validation. If the intended use of the IMD-W system is as a process monitoring and control tool only, with no change to approved conventional testing, an IOQ and tests to establish appropriate alert and action levels may be sufficient to move forward with implementation.

If a reduction in traditional monitoring is the objective, a more extensive system qualification is needed. The planned use and internal requirements should be considered when determining the level of qualification testing to be performed. The table below contains examples illustrating how the extent of testing may vary depending on the intended implementation.

Document Description and Purpose

Installation and Operational Qualification (IOQ)

Once the IMD-W system is received, an IOQ is performed to confirm it is installed and operating in accordance with applicable user, design and functional specifications, as well as manufacturer's recommendations, such that end-user requirements are met. The installation qualification (IQ) verifies the proper delivery/installation of the equipment along with the accuracy and completeness of the equipment documentation. The operational qualification (OQ) provides a test and inspection plan that verifies both hardware and software operate within the normal operating ranges required for intended use.

Performance Qualification (PQ)

The purpose of the PQ is to provide a means of ensuring and documenting that the IMD-W system is performing as intended and is fit for use in the final installation environment. This includes verification of system

	Process Control and Monitoring Tool	Supports Decision Making / No Change to Current Monitoring	Reduction in Conventional Testing
IOQ	✔	✔	✔
Determine Baseline	✔	✔	✔
Establish Alert and Action Levels	✔	✔	✔
PQ		✔	✔
Extended Side-by-Side Monitoring		✔	✔
Method Validation		Limited	✔

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operation, biologic detection and interferent discrimination performance through use of biologic- and interferent-surrogate fluorescent beads, a comparison of IMD-W online- vs. plate-count testing, and 21 CFR Part 11 compliance. The BioVigilant PQ does not contain any procedural steps for microbial challenge testing, and instead, relies on BioVigilant's published testing.

Method Validation

The Method Validation protocol includes experiments and acceptance criteria needed for the laboratory method validation of the IMD-W system. The method validation is intended to demonstrate that the IMD-W system is at least as suitable as the current plate-count test in place, and is suitable for intended use. This includes steps needed to challenge the IMD-W system using a variety of microorganisms and a commercially-available fluorescent bead standard. The validation follows guidance set forth in the European Pharmacopeia Chapter 5.1.6[1], United States Pharmacopeia <1223>[2], and the Parenteral Drug Association's Technical Report #33[3].

Testing Progression and Options

After IOQ execution, the following testing and steps may be indicated depending upon the planned implementation of the IMD-W system.

Determining a Baseline for Initial Alert and Action Levels

Gathering baseline count data is one of the first steps after selecting a loop location, completing the installation and performing an IOQ. Baseline counts are often unique to each water system and can depend upon its characteristics such as loop age, material of construction, water quality, and location of the system on the loop. As baseline total particle and biologic count data are collected, this data can be compared to other data signals available on the loop to better understand baseline counts and impacts caused by other activities occurring on the loop. For example, it can be useful to investigate counts during time periods where water is not in use (e.g. sanitization periods) to determine if counts are outside the standard baseline during these times. The table below offers some examples of considerations and their progression when establishing a baseline.

Side-by-Side Testing and Performance Qualification

If more extensive side-by-side testing is desired, many technology users perform at least one month of continuous monitoring with the IMD-W system and increased, up to daily, monitoring with the traditional method (e.g. grab samples). This provides a larger dataset for comparison of the two methods, and allows for a comparison of any trends observed with each technology. The initial IMD-W alert and action levels are applied to this data and reassessed with the goal of ensuring that the IMD-W system does not miss a trend or out-of-specification event identified by the traditional method. Similarly, the alert and action levels, and their time- or frequency-based implementation, can be updated if more or less sensitive alert parameters are desired. Side-by-side testing is part of the BioVigilant PQ template, which also can be performed at this point.

Collect Baseline Data →	Analyze Baseline Data →	Implement Alert & Action Levels
Time based on need to capture variability (e.g. 3+ months)	*Assess periods where water is not in use (e.g. during sanitization)*	*Apply initial alert and action levels to previously gathered data (e.g. 3+ months)*
Sample continuously with IMD-W system	*Identify, justify, and remove periods of data that should not be included in establishing baseline counts (e.g. during sanitization)*	*Assess the times when an alert or action level has been exceeded (e.g. How long were counts above the alert or action level?/ Did counts exceed these levels often over a short time period?).*
Collect data from other signals/sources on the loop for comparison (e.g. CFU, % tank fill, sanitization)	*Determine baseline particle and biologic counts levels*	*Assess traditional plate count results. Were these also higher than established alert and action levels during the 3-month period?*
Investigate activities on loop that impact total particle and biologic (AFU) counts	*Establish initial alert and action levels (e.g. +2/+3 Std. Dev.)*	*Determine if frequency-based or time-based alert and action levels would be more appropriate.*
		Update IMD-W alert and action levels, if needed, based on this initial implementation and data check. Reapply new levels to the data to confirm.

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Extended Side-by-Side Testing

Certain end users, for example those with a goal of reducing traditional monitoring, extend side-by-side testing for twelve months, particularly if there is a need to assess whether or not seasonality impacts baseline counts. In instances where the IMD-W alert or action level is exceeded over this period, the traditional method should be performed for comparison and, where possible, a determination made on the cause of the out-of-specification event. Also, users should strive to determine the cause of any observed baseline shifts which may be influenced by seasonality, sanitization cycles, or other events. Initial alert and action levels should continue to be in place throughout this testing to confirm their reasonableness or inform updates to them as indicated by the data and desired level of sensitivity. At some point during this testing, or before, users should consider requesting a meeting with the local regulatory agency to review the testing plan and data obtained.

Method Validation

The Method Validation should be performed once a good understanding of the IMD-W operation in its final environment is obtained and intended use is confirmed. The BioVigilant Method Validation template follows guidance set forth in the European Pharmacopeia Chapter 5.1.6, United States Pharmacopeia <1223>, and the Parenteral Drug Association's Technical Report #33. Yet, the extent of testing performed is dependent upon the final implementation of the IMD-W system and the users' internal requirements. Options for use of fluorescent beads to assess linearity and operational range are included, along with testing of all USP<1223> metrics with an assortment of microorganisms. It may be possible to use microbial challenge data provided by BioVigilant to support the end-user testing performed, which may include unique facility isolates, for instance.

Conclusion

- The extent of OWBA qualification testing performed is dependent upon the final implementation of the system, internal requirements, and confirmation discussions with the local regulatory authority.
- This testing may be far less involved for those implementations where the OWBA system is added as a supplementary tool and no changes are being made to the traditional monitoring in place.
- This document has summarized steps and testing that should be considered and the document templates available to support testing and implementation of BioVigilant's IMD-W system.

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[1] USP.2015. <1223> Validation of Alternative Microbiological Methods. United States Pharmacopeial convention. USP 38/NF33:1439

[2] Pharmeuropa. 2015. Chapter 5.1.6 Alternative Methods for Control of Microbiological Quality, European Directorate for the Quality of Medicines and Health Care. 27.1:8

[3] PDA. 2013. Evaluation, Validation and Implementation of Alternative and Rapid Microbiological Methods, Technical Report No. 33, Parenteral Drug Association

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