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RE: Flat Paddle Samplers and Contact Plates in the Compounding Pharmacy Environmental Monitoring Program

To Whom It May Concern,

Attached please find a literature review of the use of flat paddle samplers and contact plates in environmental monitoring. This overview was written at the request of QI Medical, and reflects best science at the time of writing.

FDA and USP both agree that the purpose of environmental monitoring is to demonstrate that the facility is operating in a state of control at the time of compounding. This demonstration requires frequent sampling, strong microbial growth in the recovery agar and appropriate analysis of the data.

There is no evidence in the literature that Soybean Casein Digest Agar behaves differently when presented in a flat paddle sampler versus a contact plate. Evidence in the peer-reviewed literature supports the conclusion that these two sampling devices are equivalent. There is, however, some evidence to suggest that the packaging of the flat paddle sample may allow longer, more convenient storage conditions before use and greater ease of use during sampling. This relative advantage may explain the obvious success in the marketplace for the flat paddle sampler in the compounding pharmacy (see Figure 1)

FDA provides specific guidance on environmental monitoring in its “Aseptic Processing Guide” (2004) and USP provides information in chapter <1116> “Microbiological Control and Monitoring of Aseptic Processing Environment”. The peer-reviewed literature has been summarized in the following report. There is no indication that either the regulatory or the peer-reviewed literature preferentially supports the use of either the flat paddle sampler or the contact plate as a “compliant” testing device in the compounding pharmacy.

Thank you for the opportunity to contribute to this discussion.

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Devices Used for Environmental Surface Sampling in the Compounding Pharmacy

Abstract

This literature review is intended to provide an overview of the relative effectiveness of commonly used devices in environmental monitoring for the pharmacy.

The purpose of environmental sampling in the compounding pharmacy is to monitor the state of control of the clean room environment. This requires frequent testing and diligence. The sampling devices most commonly used are contact plates and flat paddle samplers, both of which rely on agar growth media projecting above the device. The agar is pressed onto the surface and microorganisms adhering to the agar surface are captured for subsequent growth and analysis. Devices that use well established and compliant growth media (supported by USP and/or FDA) are acceptable for this purpose.

Flat paddle sampling devices and contact plates both have a long and varied history of use in microbiological sampling. Published studies have shown them to be similar in effectiveness. There seems to be little to distinguish among them in terms of efficacy, rather the choice is driven by facility needs. The flat paddle sampler design seems to be the clear preference in compounding pharmacy settings, based on recent independent surveys (Figure 1.)

The Purpose of Environmental Monitoring

The most important consideration in determining how to execute an environmental monitoring program is to clearly define its purpose. FDA has made its expectations clear in the 2004 Aseptic Processing Guidance document (FDA 2004) in section X.A.1 where it is stated:

> "In aseptic processing, one of the most important laboratory controls is the environmental monitoring program. This program provides meaningful information on the quality of the aseptic processing environment (e.g., when a given batch is being manufactured) as well as environmental trends of ancillary clean areas. Environmental monitoring should promptly identify potential routes of contamination, allowing for implementation of corrections before product contamination occurs (211.42 and 211.113)."

And in X.A.2: "Environmental monitoring data will provide information on the quality of the manufacturing environment."

USP reinforces this point in Chapter <1116> (USP 2014) where it is stated:

“Routine environmental monitoring should provide sufficient information to demonstrate that the aseptic processing environment is operating in an adequate state of control. The real value of a microbiological monitoring program lies in its ability to perform consistent, high-quality environmental conditions at all times.”

If microbiological monitoring is to be of value, how can this data be best used? FDA suggests that trending frequently collected data is the method of choice:

"Trend analysis of microorganisms in the critical and immediately adjacent areas is especially helpful in determining the source of contamination in a sterility failure investigation. Consideration of environmental microbial data should not be limited to results of monitoring the production environment for the lot, day, or shift associated with the suspect lot. For example, results showing little or no recovery of microorganisms can be misleading, especially when preceded or followed by a finding of an adverse trend or atypically high microbial counts. It is therefore important to look at both short- and long-term environmental trend analyses." (FDA 2004 - Section XI.C.3)

"The review of data and associated trends from daily monitoring of [production] personnel can provide important information indicating a route of contamination. The adequacy of personnel practices and training also merit significant review and consideration." (FDA 2004 – Section XI.C.4)

An effective environmental monitoring program for a compounding pharmacy producing sterile CSPs should involve regular sampling to permit this data trending (see USP <1116> (2014) for more information). Recently released draft guidance for 503B Outsourcing Facilities (FDA 2014a) requires daily monitoring (although FDA's draft guidance on 503A facilities is silent on this point (FDA 2014b). USP <797> describes the use of environmental sampling (monitoring) upon qualification of the clean room and PEC and in response to changes in the environment or an issue with a CSP. This is clearly out of step with current practice and is undergoing review as part of the USP rewrite of the <797> currently in progress.

Section Summary

The purpose of environmental sampling in the compounding pharmacy is to monitor the state of control of the clean room environment. This requires frequent testing and diligence. The test method used for this monitoring should be:

- Easy to store
- Stable on storage
- Simple and effective in use
- Easy to read and interpret

The Sampling Devices

USP discusses sampling devices in Chapter <1116> (USP 2014) where it is stated:

"Surface sampling methods are also not standardized. Different media are employed. In general, surface monitoring has been found to recover <50%, even when used with relatively high inoculum levels on standardized coupons."

There are two methods commonly used to sample pharmacy surfaces for microbial contamination. The first involves contact plates. The contact plate is based on a small petri dish that is overfilled with agar medium, resulting in the agar projecting above the lip of the plate. This agar projection is pressed onto the surface to be tested, and a sample of the microbes on that surface are transferred to the surface of the agar.

The second method of surface sampling commonly in use is the flat paddle method. This method is employed by the Hygicult and the EnviroTest devices (EnviroTest, marketed by QI Medical, shown). This method is fundamentally the same as the contact plate, except that the agar medium projects above both sides of the paddle, allowing both sides to be used. The paddle is aseptically stored in the screw-top container. This point is important to consider, as the screw cap closure allows for greater stability on storage in comparison to the relatively open design of the contact plate (which allows rapid desiccation of the growth medium). In addition, the rectangular shape of the flat paddle sampling device allows greater ease of sampling in corners compared to the round contact plate.

The flat paddle device is widely used in the pharmacy, as recent surveys have shown (see Appendix 1 – QI Medical markets the EnviroTest flat paddle sampling device.)

Flat Paddle Sampler Equivalent to Contact Plate

Flat paddle sampling devices have been shown to be equivalent in efficacy to the round contact plates. In a pair of studies by Salo's group at the VTT Technical Research Centre of Finland (Salo 2000, Salo 2002) compared the efficacy of the rectangular flat paddles, circular contact plates and swabbing methodology.

The first study was a collaborative effort among 12 sites evaluating total aerobic microbial recovery using Soybean Casein Digest Agar as the recovery medium (see discussion of media below). This study compared the Hygicult® TPC dipslide (a flat paddle sampler marketed by Orion Diagnostica) against contact plates and swabbing. The challenge used stainless-steel surfaces artificially contaminated with different microbes at various levels. The Hygicult TPC dipslide, contact plate, and swabbing methods gave similar results.

The second study (Salo 2002) was a similar collaborative study, but in this case with *Enterobacteriaceae* to compare Hygicult® E dipslides with violet red bile glucose agar (VRBGA), contact plates and swabbing. They used stainless steel surfaces to determine recovery of enteric bacteria. The results of this sudy were the same as in the Salo 2000 study - no significant differences were seen between the sampling methods.

Flat Paddle Samplers Are Widely Used

These devices have been in use for many years (Walter 1955, Hakalehto 2006) for a variety of purposes. Their use in pharmaceutical clean rooms is well established (PDA 2014, FDA 2004) as is the use of sampling paddles and contact plates in compounding pharmacies (Anon 2013, Anon 2014, Weissfeld, A. & P. Vance. 2008). In fact, recent surveys show they are currently in widespread use in the pharmacy environment (see Appendix 1).

In addition, use of these methods have been reported in the literature for sampling in a variety of applications including:

- Food production facilities (Lehto 2011)
- Textile Plants (Fijan, S *et al*, 2008)
- Poultry Plants (Russell, SM et al, 1997)
- Bioburden testing of cannabis (Nykter 2007, Salo, Kymalainen, H-R *et al*, 2005)

- Cave Walls (Gonzalez 1999)
- Dairy Farms (Carrascosa 2012)
- Cheese factories (Salo, S and G Wirtanen, 2007)
- Slaughterhouses (Rahkio, M. and H. Korkeala, 1997)
- Sanitary Studies of Homes (Toiviainen-Laine, E et al, 2009)
- Library Collections (Zereck 2010)

The Media

The microbial growth media used in monitoring is critical to the success of recovery. Both contact plates and flat paddle sampling devices use the same mechanism of recovery – pressing the agar surface to the surface to be sampled and then lifting it away, removing microorganisms adhering to the agar surface. Since there is no difference in the basic method, the media used in the recovery becomes an important consideration. It can generally be expected that any sampling device that utilizes suitable recovery media will behave as do other recovery devices using that same or similar growth media.

USP <1116> (USP 2014a) recommends the use of Soybean Casein Digest medium as "…suitable for environmental monitoring in most cases because it supports the growth of a wide range of bacteria, yeast, and molds. This medium can be supplemented with additives to overcome or minimize the effects of sanitizing agents or of antibiotics."

This last point is important as much of the clean room environment is contaminated by residue from sanitizing agents. Most surface sampling media now include a variety of these additives to neutralize the residual sanitizer (see USP <1227> USP 2014c) for a more complete discussion of these additives and their value).

Soybean Casein Digest Agar was first described as a rich nutrient growth medium for clinical studies (McCullough, NB, 1949). It is now well-established as a general-purpose recovery medium for bacteria, yeast and mold (USP 2014a) and is recommended in FDA's Bacterial Analytical Manual (FDA 2001). Soybean Casein Digest Agar also goes by the abbreviation SCDA and the synonym Trypticase Soy Agar (TSA).

There are some situations where a selective medium is desired for preferential recovery of yeasts and molds. The critical aspect of a selective agar in microbiological studies is that the agar is inhibitory in some regard. This inhibitory characteristic affects different microorganisms to varying degrees. For example, bacteria have significant difficulty growing in low pH environments. Yeasts and mold are far more resistant to low pH and are able to grow well under these conditions.

Two selective agars are commonly used in surface monitoring that take advantage of this differing response to low pH. Malt Extract Agar (MEYAM) was developed as a fungal recovery medium with a pH of 5.4 ± 0.2 (FDA 2001a) and Sabouraud Dextrose Agar (SDA) as a fungal recovery medium with a pH of 5.8 ± 0.2 (FDA 2001c).

It must be noted that the commonly used sampling paddles and contact plates both use the same media. The choice of which to use is based on facility preference.

Section Summary

The sampling device depends on supporting good microbial growth for its efficacy – therefore a nutritive growth medium is critical. Devices that use media listed above (supported by USP and/or FDA) are acceptable for this purpose.

Summary

There seems little to distinguish between flat paddle samplers and contact plates in terms of efficacy.

- Published studies show them to give similar results
- Both use Soybean Casein Digest Agar, or other nutritive growth media recommended by FDA and/or USP

Flat paddle samplers are widely used, especially in today's pharmacies. This may be because of their convenience in use and long storage life

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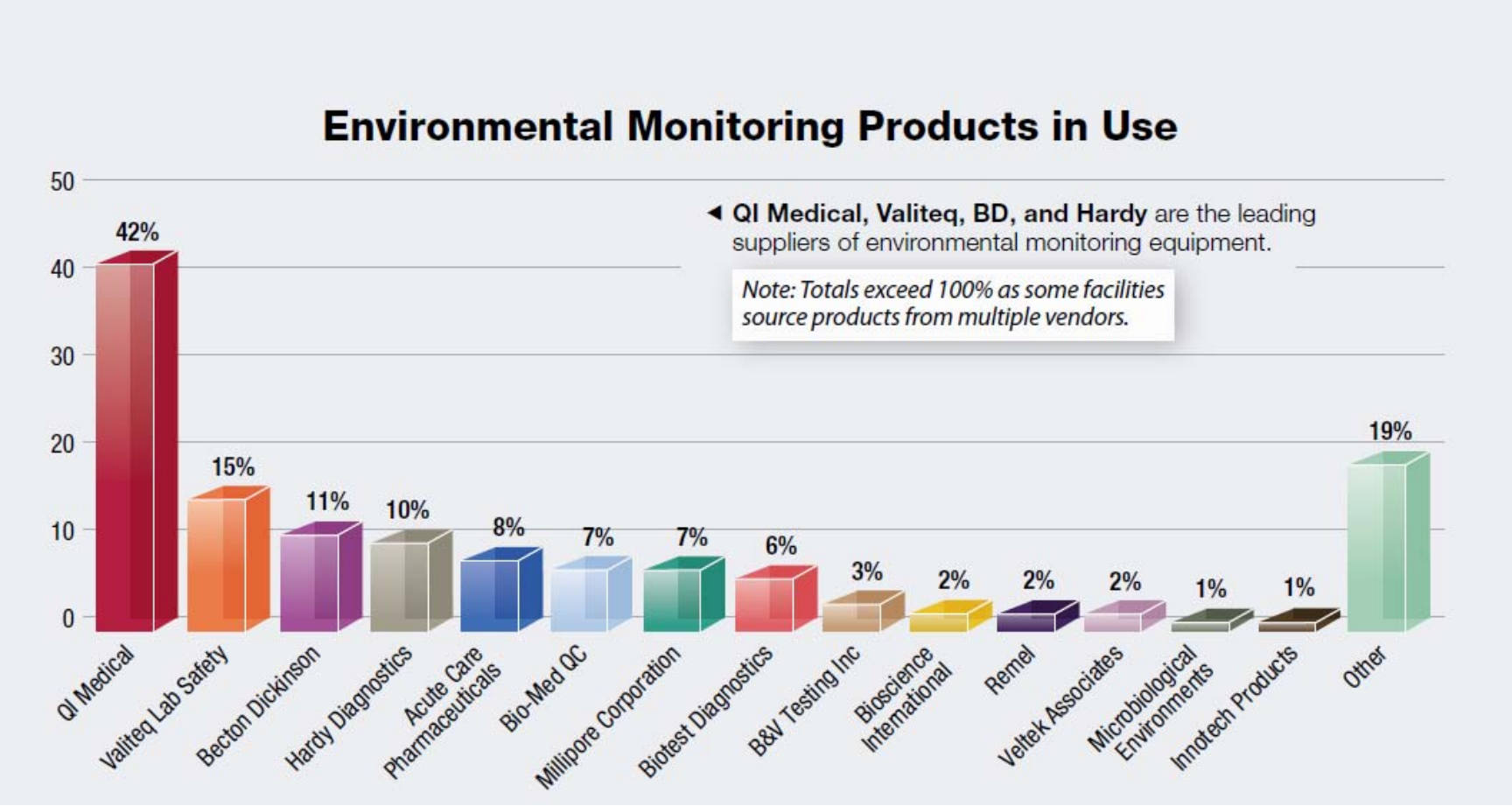
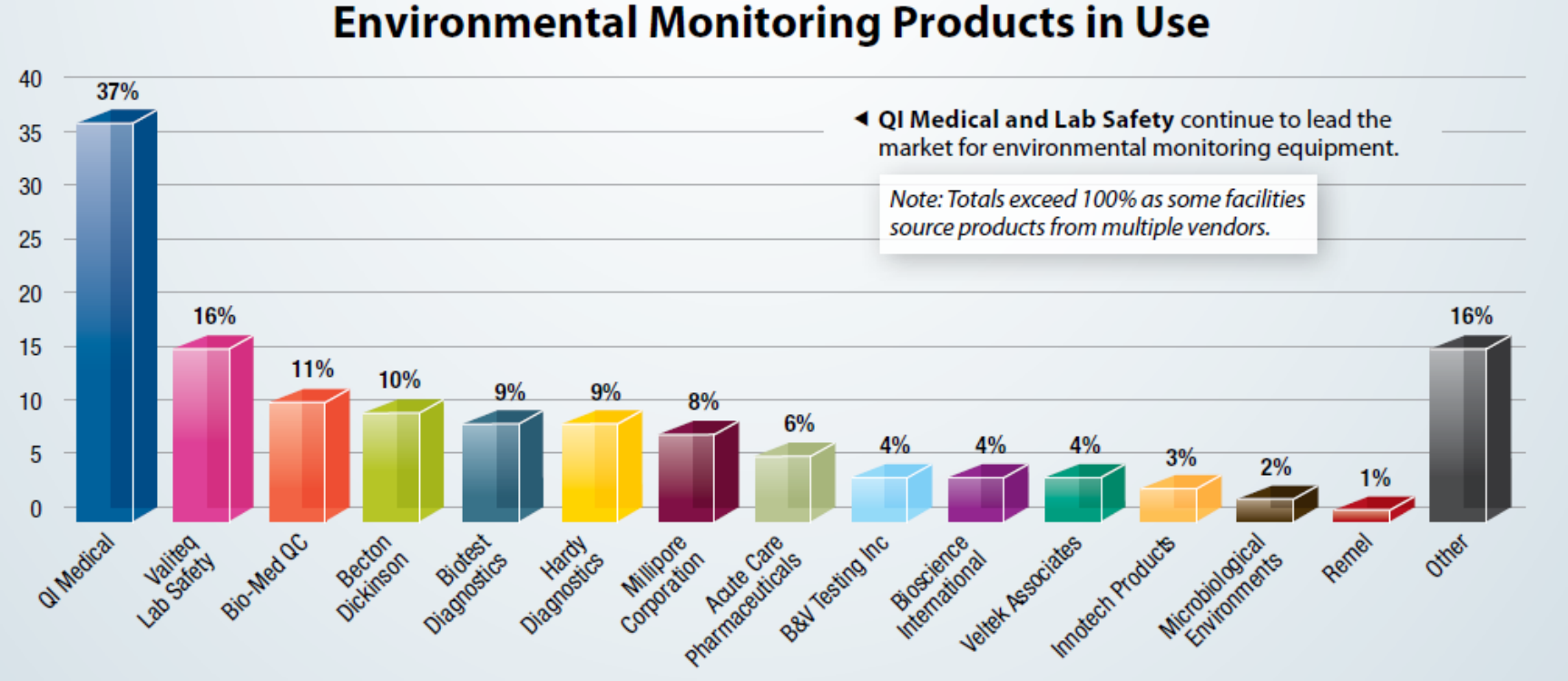
Appendix 1. EM Products in Use 2013-2014

2014



From Anon. 2014. Environmental Monitoring. *Pharm Purch Prod* 11(4 - State of Pharm Compounding):s28-s29

2013



From Anon. 2013. Environmental Monitoring. *Pharm Purch Prod* 10(4 - State of Pharm Compounding):s30-s31