A Discussion of Alternative Methods for Environmental Monitoring Trend Evaluation

Background

The environment in which pharmaceutical products are manufactured and prepared is critical to the quality of products produced, and therefore the safety of the patients to which they are administered. As a result, the cleanliness of the environments is monitored using a combination of techniques, including viable and non-viable environmental monitoring. Viable environmental monitoring programmes may include a number of methods such as settle and contact plates, active air sampling, swabs and personnel monitoring including finger dabs and gowning monitoring. Regardless of the methods used, these techniques generate data sets which must be reviewed and interpreted in order to identify whether the environment remains in a state of control or not.

Because these methods require organisms to grow on the media during a period of incubation, and may not arrive at the microbiology laboratory for a number of days after they had been exposed, results are often not available at the point of release of products which were prepared in a given monitoring session, this is especially true for doses prepared under Section 10 exemptions, radiopharmaceuticals, some ATMP manufacture, and may also be the case for Specials which have a particularly short shelf life which necessitates release prior to availability of EM data.

As a result of the criticality of environmental control, there is a requirement for units to routinely review the EM data and address any adverse performance at the earliest opportunity. There are several statistical methods which are used to interpret EM data, these will be discussed and considered against the requirements of a robust trend analysis system.

Existing Methods

Action and Alert Limits

On a basic level, action and alert limits are applied. The maxima for action limits are defined in Annex 1[1], and sites are required to apply appropriate methodology to determine relevant limits. This is applied in a variety of ways, either per plate, group of plates, or across a whole site (dependant on the grade and type of plate).

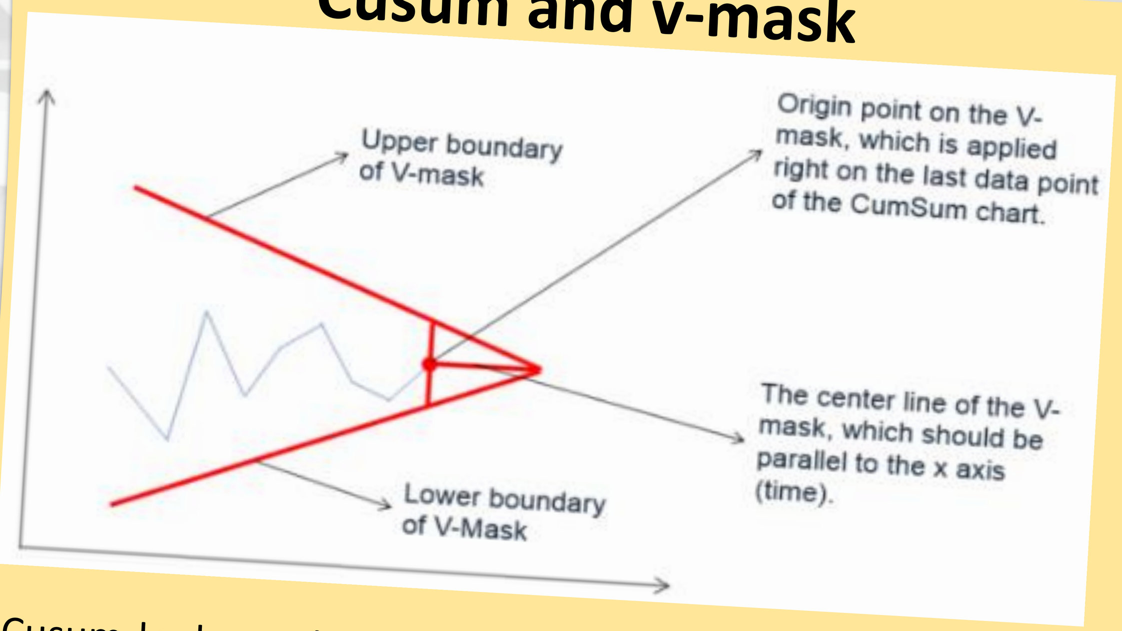
Some sites use mean + 2σ for alert limits and mean + 3σ for action limits. These may be calculated across a range of plates and time periods, and upper and lower bounds are sometimes applied.

Moving Average

Moving Averages are useful to help visualise whether over a period of time average counts are increasing, decreasing or remaining static. Several other factors must be considered:

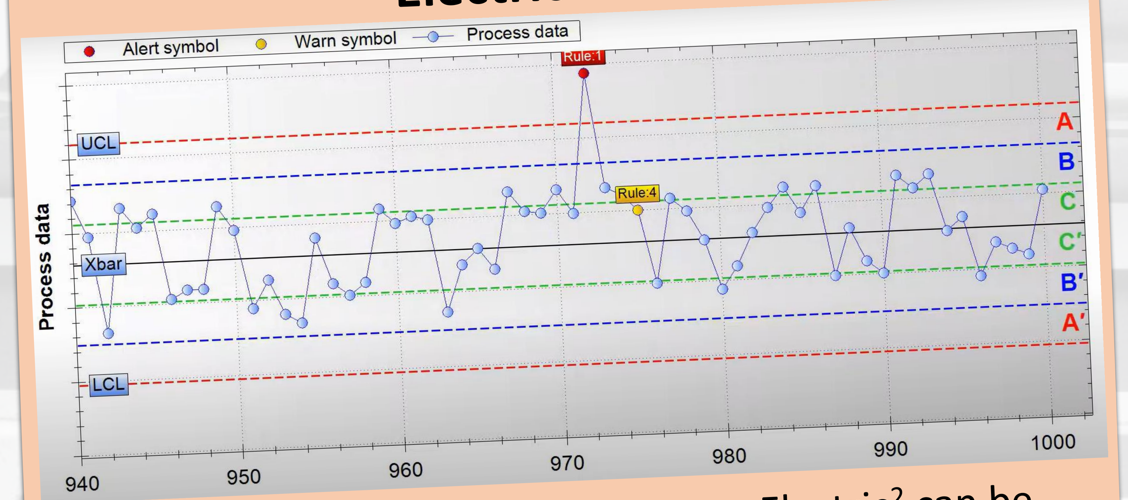
- How long should the average be taken over?
- How may plates should be considered?
- What is the impact in operation vs. at rest monitoring?
- Should more recent data be more important (exponential moving averages)
- What is the threshold at which action needs to be taken?

Cusum and v-mask



Cusum looks at the 'direction of travel' and can be useful in identifying a plate going out of control. If applied to groups of plates the metric may not detect an adverse trend. Users need to define parameters to ensure the tool is sufficiently sensitive.

Shewart Chart (Process Control) and Western Electric Rules



A series of rules established by Western Electric[2] can be applied to process control charts (Shewart Charts) that identify abnormal trends in a data series. Evaluation of EM data would be time consuming unless automated, and must be applied to individual data sets rather than pooled data.

General Failure Plate Rates Operator Server (disinfector)

Plate location growths alone are not the only factor to consider when reviewing data for adverse trends. A major factor to consider is operator or server, as any adverse trends may move with the operator rather than trigger a trend warning based on a plate location.

Evaluation of operator or server trends is ordinarily done by review of all plates associated with an individual acting in each role. This may be automated or include data manipulation using spreadsheets etc.

Organism Identification

As well as EM counts, the identification of organisms may indicate an adverse trend. As all grade A and B plates must be identified to species level, and with modern rapid identification systems, this dataset can provide insight into issues and should form part of any trend analysis. As with operator failure rates, this is often a manual process and may require data manipulation.

Data Integrity

Regardless of the methods chosen, any manipulation of primary data represents a data integrity risk. Systems used to capture EM data would ideally perform trend analysis automatically and alert site personnel when data indicates a potential loss of control. The use of spreadsheets to manipulate data outside of a validated system is bad practice and should be avoided where possible.

Discussion

Each method has its benefits and limitations. Western Electric rules offer a number of techniques to identify early signs of an adverse trend, although not all may be suited to EM data (e.g. 15 consecutive results within 1σ of the mean). Additionally, identification of organisms is an important factor; it may be beneficial to evaluate trends in bacteria and moulds separately as it is likely sites will be more concerned where repeated low levels of mould are identified in a facility rather than similar bacterial counts.

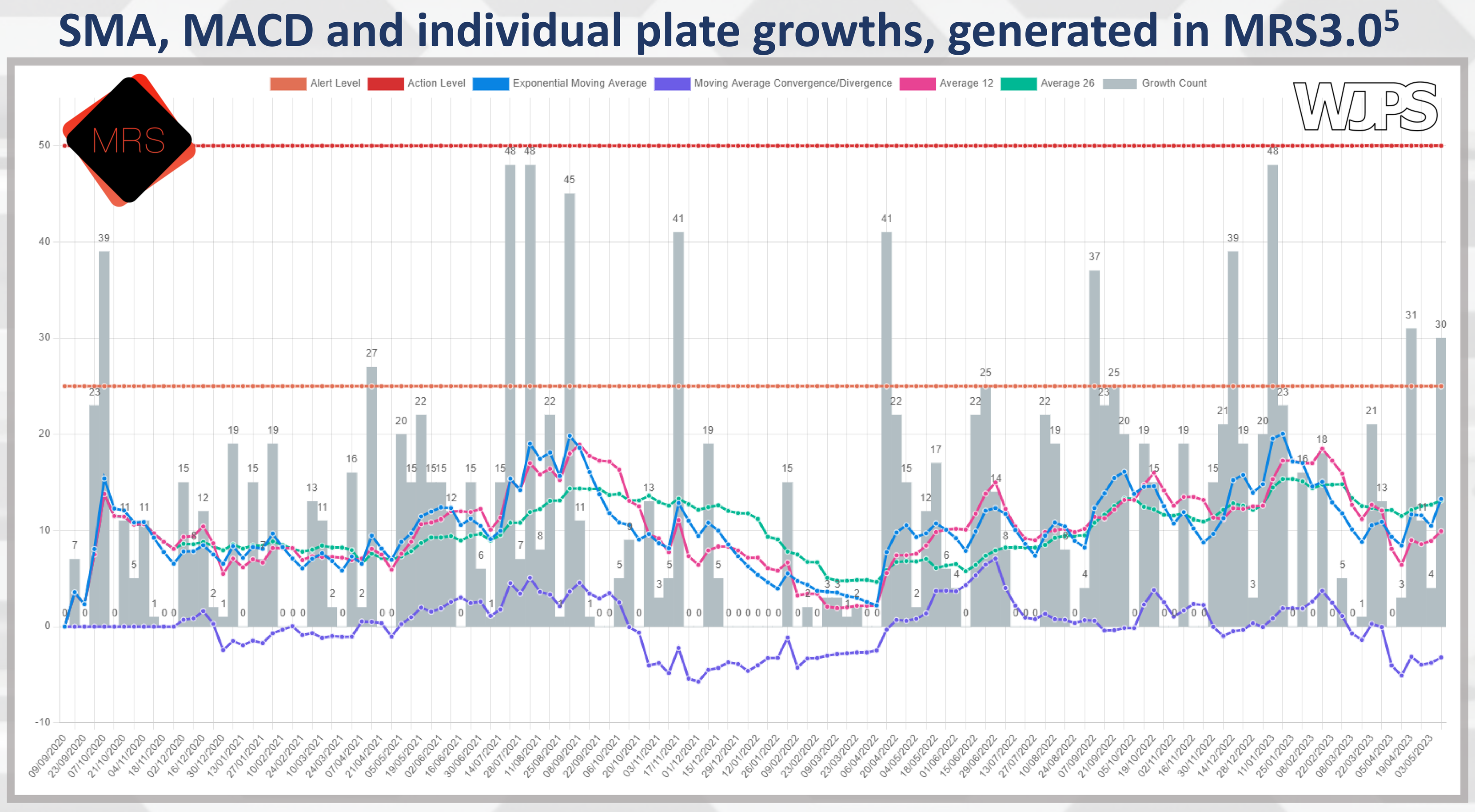
Finally, the occupancy state of monitored areas is an important consideration. Routine (e.g. weekly) monitoring carried out on a day with little or no activity is unlikely to be comparable to routine monitoring carried out on a day of normal or increased activity in lower grade areas (e.g. monitored CNC, Grade D or Grade C). The ability to identify activity levels for these areas may allow more sensitive trend analysis tools to be deployed.

Other industries where identification of change in a dataset is important could provide alternative approaches to trend analysis, with a view to implementing an automated 'Early Warning System'. Financial markets are a prime example of an area where early identification of the beginning of a changing trend are critical. Tools which expand on the methods above (exponential moving average - EMA) and determine how rapidly a change is occurring can be used. Moving Average Convergence/Divergence, MACD[3] (pronounced Mack-Dee) may provide a useful metric and could be automatically applied to EM data.

MACD traditionally uses two EMAs over differing periods (ordinarily 12 and 26 data points), and evaluates the convergence or divergence of the two. When a positive value is seen, this indicates the short term (12 point) moving average is above the long term (26 point) moving average. The greater the MACD value, the faster the change is occurring. Taking the MACD value further, a simple moving average (SMA) of the MACD value can be added, where this value remains positive, it indicates a worsening trend. Modified versions of the MACD metric may use SMA rather than EMA. Whilst MACD only looks at a single data set, algorithms considering other plates in adjacent locations could also be developed. An example of MACD, EMA and SMA when applied to settle plate results from a Grade D cleanroom are shown in figure 2.

Further work is required to establish appropriate parameters for MACD (e.g. short- and long-term EMA periods, use of EMA vs. SMA, SMA period for MACD, and the signal values for either MACD or SMA-MACD, and application across different organism types. Once established, these metrics can be used to develop an 'Early Warning System' incorporated into EM reporting software. This will, of course, require qualification before deployment.

Figure 1: EM data from a single Grade D Settle Plate showing EMA, SMA, MACD and individual plate growths, generated in MRS3.0[5]



Conclusions

Several methods for trend evaluation of EM data are available, but no overall consensus exists in terms of an established methodology.

MACD offers a useful metric and work is required to refine the method and establish appropriate signal parameters to establish a 'live' early warning system. Trend analysis must also consider organism type, surrounding EM locations and operators.

Due to the complexity of the data analysis required, and the need for early detection of potential adverse trends to allow early intervention, automated data integrity compliant systems are required. The conclusions drawn from this review of available methodologies may form the basis of a URS for an automated trend analysis system.

These aspects should be further explored with proposed parameters tested on historical data to confirm warnings are raised early enough to allow intervention, without 'false alarms' to reduce the risk of alarm fatigue[4].

References: 1. **European Commission.** Annex 1: Manufacture of Sterile Medicinal Products. *The Rules Governing Medicinal Products in the European Union Volume 4 EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use.* [Online] 08 22, 2022. [Cited: 08 14, 2023.] https://health.ec.europa.eu/system/files/2022-08/20220825_gmp-an1_en_0.pdf 2. **Grimes, Adam.** The Art and Science of Technical Analysis: Market Structure, Price Action, and Trading Strategies: Wiley, 2012, Appendix B, pp. 409-424. 3. **Western Electric.** *Statistical Quality Control Handbook.* Indianapolis : Western Electric Co., 1956. 4. **Woo M, Bacon O.** Alarm Fatigue. In: Shoemaker-Hunt S, Hoffman L, et al. Hall KK. *Making Healthcare Safer III: A Critical Analysis of Existing and Emerging Patient Safety Practices [Internet].* Rockville : Agency for Healthcare Research and Quality (US), 2020.
5. MRS3.0 Developed by WJP Software Ltd. www.wjps.co.uk

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