Investigation into Rapid Microbial Detection Methods (RMM) to improve the QA of NHS manufactured aseptic products

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Introduction

Real time microbial monitoring using alternative rapid microbiology methods (RMM) has been used in the food and pharmaceutical industry for many years. It has recently been demonstrated to have potential within NHS QA aseptic activities[1]

Current QA on aseptic batches are often broth runs which are assessed retrospective at 7 and 14 days. RMM have the potential to give “real time” responses.

Methodology in the earlier NHS evaluation[1] has been developed to address previous limitations. Results from this definitive spiking study to compare traditional recovery using TVC[2] and RMM results are presented here.

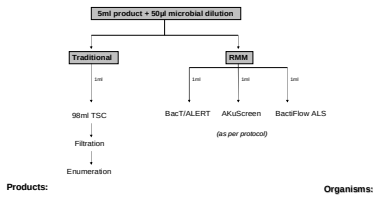
Subsequent commercial RMM developments are in progress and are examining compounds which have proved problematic in this study

Aims

This study aims to definitively evaluate three different RMM for their ability to improve the QA processes associated with NHS aseptic manufacturing.

Method

Concordance
A spiking study was carried out in a Grade A environment where 50µl of four micro-organisms were each spiked at low levels into four aseptic products. Traditional methods of QA microbial recovery, as described in the BP[1] were compared with results from the three RMM after 10 mins exposure to the product.



Products:
Heparin 100u/ml
Parenteral nutrition 7.5%
Vancomycin Inj 10ml/2ml
Methotrexate Inj 15mg/0.6ml

Organisms:
S.aureus
P.aeruginosa
B.subtilis
C.albicans

Method (continued)

1	2	3
BacT/ALERT®	AKuScreen®	BactiFlow ALS®
CO_2 generated colour changes	ATP bioluminescence	Direct fluorescent labelling



Results

Concordance
All products passed a feasibility test with each RMM indicating that these rapid methods could be suitable for QA microbial testing.

Table 1 presents cost and time to results data for each RMM[1] together with a summary of overall % concordance between TVC and RMM. Table 2 shows the complete concordance data.

All three RMM systems are able to provide 100% concordance when used to detect contamination in PN and Heparin within their recommended time frames (Table 1). At 24hrs, BacT/ALERT only had difficulty recovering yeast species and this may be overcome by dual temp incubations. All RMM had problems recovering Gram positive organisms from Vancomycin and Methotrexate. Each company was invited to investigate and develop their protocols.

Overall the BacT/ALERT system was technically the easiest to use and had the highest concordance after 3 days.

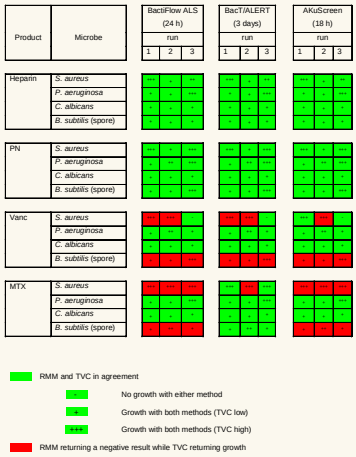
Commercial Development
Celsis and AES Chemunex have both identified that a filtration and washing step, prior to incubation, overcomes the problems of recovering Gram positive organisms from Vancomycin and Methotrexate.

Results (continued)

Table 1 – Summary

	Traditional	BactiFlow ALS®	AKuScreen®	BacT/ALERT®	
Time to result	7-14 days	24hr	18hr	24hr	3days
Concordance	100%	78%	79%	67%	88%
Cost (test batch)	£75	£122	£98	£71	

Table 2 – Concordance Patterns



Conclusion

All three RMM systems provided full concordance with traditional TVC methods for PN and Heparin within the commercial recommended time frames.

The BacT/ALERT® system was technically the easiest to use, cheapest for this test run and highest concordance when results were read after 3 days. Concordance levels were the lowest when this system was used within 1 day, however dual temp incubation is likely to improve this recovery rate.

All three RMM systems had problems recovering Gram positive organisms from vancomycin and methotrexate, however Celsis and AES Chemunex have demonstrated that inclusion of a filtration step prior to incubation overcomes this. bioMerieux are currently investigating the use of charcoal FANS within their incubation vials.

The results of this study demonstrate that RMM can improve QA of selected NHS manufactured aseptic products.

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References

1: Hiom S. et al (2010). Investigation into rapid microbial detection methods (RMM) to improve the QA of NHS manufactured aseptic products. *Int. J. Phar. Pract.* **18** (Suppl 2) 92.
2: British Pharmacopoeia. Appendix XVI B: Microbiological Examination of Non-Sterile Products. 2009. HMSO: London.