

Monitoring aseptic units — a microbiology audit tool

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Pharmacy aseptic units should monitor the quality of services provided to them by external suppliers. This article describes an audit tool developed by one hospital manufacturing unit that has been used to confirm the reliability of environmental monitoring carried out by an external laboratory



The environment in which an aseptic product is prepared is critical to the quality of the finished product

Aseptic preparation of medicines in hospital pharmacy units usually comprises the combination of licensed sterile ingredients in a manner that will ensure that the resulting product, in its final container, is sterile. One of the inherent weaknesses of this activity is that aseptically prepared medicinal products cannot be tested for sterility as would normally be the case for other sterile manufactured medicines. There are two reasons for this. First, such preparations are usually prepared as single items for individual patients. If the product were to be subjected to the pharmacopoeial test for sterility there would be no medicine left to administer to the patient. Second, and perhaps less obviously, a sample for sterility testing cannot be taken without compromising the integrity of the final container (eg, the syringe) thereby exposing the remainder of the medicine to possible microbial contamination.

The pharmacist responsible for releasing the medicine therefore relies upon the overarching quality assurance systems in place to ensure that the medicine is sterile. Good quality assurance systems include

appropriately trained staff working in accordance with validated procedures, using tested and calibrated equipment, and undertaking aseptic preparation in a clean environment that is routinely monitored.

Standards have been set for the microbiological cleanliness of the immediate (and background) environment in which the manipulation of aseptically prepared medicines occurs.¹ The maintenance of a suitably clean working environment is assessed via a programme of routine environmental monitoring of both physical and microbiological parameters. The minimum frequencies for such monitoring have been established for the NHS.²

In most hospital pharmacy aseptic units, microbiological environmental monitoring is undertaken by pharmacy staff. However, in my experience, there is a lack of pharmaceutical microbiology expertise most units so the identification of any contaminating microorganisms detected is often carried out by an outside agency. This may be the hospital's own microbiology laboratory or a laboratory belonging to the Health Protection Agency (HPA). In some cases the laboratory might incubate the settle plates, contact plates, swabs and broth cultures for the pharmacy aseptic unit and may also prepare and provide the media used by the pharmacy staff to monitor the environment.

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	Management	Audit result yes/no/partial	Review or assess by scrutiny of the following	Comments
1	A signed service level agreement (SLA) is in place and in date		Documentation	
2	The SLA outlines what services are provided by the microbiology laboratory		Documentation	

Figure 1: Example of the layout of the audit tool

Panel 1: The audit tool

Following are the areas that are assessed in the proposed audit tool, which would be presented as shown in Figure 1 (p130).

Management

- A signed service level agreement (SLA) is in place and in date
- The SLA outlines what services are provided by the microbiology laboratory (eg, incubation of media, identification of micro-organisms, sterility testing)
- The frequency and number of samples to be tested is specified, and arrangements for any additional work can be catered for (within specified limits)
- The SLA covers the provision of specialist advice from, for example, a consultant microbiologist

Media

- The SLA states who is responsible for the purchase or provision of the growth media used and describes the types of media required
- If the media are purchased, records show that they are assessed for quality. A certificate of analysis shows that the media are sterile and their fertility has been tested with specified pharmacopoeial reference strains
- If the media are made in the laboratory and poured into plates on site:
 - An audit trail for the sterilisation of empty Petri dishes is available
 - Pharmacopoeial formulae are used to prepare the media
 - Worksheets (completed at the time of preparation) detail weights and volumes used, etc
 - The media are fertility tested using pharmacopoeial reference strains
 - Plates are poured in clean conditions to prevent or reduce microbial contamination
 - Plates are sterilised (by gamma irradiation of stated dose) or are pre-incubated before use
 - The storage and dispatch of poured plates minimises the risk of contamination before use
 - A comprehensive set of standard operating procedures (SOPs) describes all the operations associated with the production of media. These are current and subject to suitable approval and review

Microbiological methods

Receipt/storage

- All plates are securely labelled on receipt into the laboratory (on the base of the plate, not the lid)
- All samples submitted to the laboratory are incubated as soon as possible. If there is any storage before incubation, a maximum storage time is specified.
- Prior to incubation samples are stored in an appropriate manner, separate to clinical specimens

Incubation

- A dedicated incubator is used rather than the pharmacy samples being incubated with clinical isolates
- The temperature of the incubators is monitored and thermometers are appropriately calibrated or checked for accuracy at least annually

- There is a programme for routine cleaning and disinfection of the incubators
- Incubation times and temperatures (with limits) are specified for each type of media submitted

Reporting

- Reports and results are to an agreed specification (eg, the number of colony-forming units (cfu) per plate for settle plates, and cfu/ml for broth)
- For specified samples or locations (eg, within the critical zone of the isolator) any micro-organisms detected will be identified to at least the level of genera

Methodology

- SOPs describe all the operations associated with the identification of micro-organisms (eg, Gram stain, spore stain, oxidase and catalase tests). These are current and subject to suitable approval and review
- Procedures and test methods comply with pharmacopoeial requirements
- Procedures and methods which have been developed in-house have been validated for efficacy, etc

Advice

- The laboratory can provide an appropriate level of expert advice in the event of unusual or out-of-specification results, trends in results or following untoward patient events
- Laboratory staff are familiar with environmental monitoring as well as clinical microbiology
- Staff from both departments can visit each others' workplace for induction/training purposes

Extra work and special investigations

- Mechanisms are in place for the pharmacy to inform the laboratory if the volume of work is likely to alter significantly
- Mechanisms are in place for the laboratory to inform the pharmacy if it is unable to undertake the agreed work. The laboratory has a contingency plan in place
- The laboratory can undertake extra work arising out of the validation of new equipment or premises or from the investigation of unexpected results

Audit/quality assurance

- Staff are adequately qualified for the tasks they are performing
- Training records show that staff are trained in the tasks they undertake and that training is kept up to date
- The SLA allows the releasing officer or responsible pharmacist to inspect the laboratory at any time (subject to convenience and confidentiality)
- The laboratory participates in external quality/proficiency monitoring schemes (eg, clinical pathology accreditation, ISO 9000)
- The laboratory is subject to formal audit (internal and external) to an agreed timescale

For each area in the tool the assessor should record whether the unit is compliant with each point. This may be checked by visual inspection of the unit (eg, to confirm that a dedicated incubator is used for the samples), or by checking that an appropriate standard operating procedure, service level agreement or other such document meets the criteria of the audit point. Other areas of the audit may be assessed by the inspection of records (eg, a log of incubation temperatures or a calibration certificate for a piece of equipment).

Given the critical importance of the environment in which medicines are prepared to the quality of the finished product, it is prudent to assess periodically the performance of the microbiology laboratory used by the pharmacy aseptic unit. Indeed, the audit of external suppliers of services should be part of the overall quality management system of any NHS pharmacy aseptic service. With this in mind an audit scheme has been devised to enable pharmacists and pharmacy technicians, who may have a limited knowledge of microbiology, to audit their own external microbiology laboratory service.

— Scope of the audit

This audit scheme should enable the auditor to establish whether or not the microbiology laboratory is operating in a manner which does not compromise the quality of the environmental monitoring results obtained, and thus the quality of the product. Although it is often assumed that microbiologists and pharmacists understand each other's professional needs, some basic misunderstandings can remain which may have a significant effect on results. For example, hospital microbiology laboratories are primarily interested in clinical microbiology and are set up to detect pathogens which prefer incubation temperatures of 37C, and

specific nutrients such as blood agar. However, the types of micro-organisms encountered during environmental monitoring may prefer room temperature incubation conditions, and more fastidious micro-organisms may not thrive at the higher incubation temperature.

A further consequence of this difference in focus is that a clinical microbiologist may not be aware that aseptically prepared medicines are usually unpreserved and may be stored for up to seven days before administration. Therefore the consequences of even low-level contamination with a non-pathogenic organism (especially in a "nutritious" product such as a total parenteral nutrition bag) can be profound.³

The proposed audit scheme is primarily based on the requirements outlined in appendices 1 and 3 of 'Quality assurance of aseptic preparative services', published by the Pharmaceutical Press.² It enables a number of activities to be assessed, as outlined in Panel 2.

Panel 1 (p131) shows the areas assessed in the audit.

— Use of the tool

Figure 1 (p130) shows an example of how this audit tool might be set out when performing the audit. The tool has been used to assess the quality and performance of the

HPA's microbiology laboratory in the East of England, based at Addenbrooke's Hospital, Cambridge. The need for such an audit arose in response to an inspection of the licensed hospital pharmacy manufacturing unit by the Medicines and Healthcare products Regulatory Agency. The unit uses the HPA laboratory as an external supplier of microbiological services, and the MHRA cited the lack of an inspection of the laboratory facility and services as a quality assurance deficiency.

The use of the audit tool was straightforward and meant that the inspection, while thorough, was completed in just over two hours. It provided reassurance that the results provided by the laboratory were reliable.

— References

1. Medicines and Healthcare products Regulatory Agency. Rules and guidance for pharmaceutical manufacturers and distributors 2007. London: The Pharmaceutical Press; 2007.
2. Beaney AM (editor). Quality assurance of aseptic preparation services. Fourth edition. London: Pharmaceutical Press; 2006.
3. NHS Pharmaceutical Quality Assurance Committee. Aseptic preparation in NHS hospitals — Information for microbiologists. London: The Committee; 2001.

Panel 2: Activities assessed in the proposed audit scheme

- The management of the service and the scope and appropriateness of any service level agreement between the microbiology laboratory and the pharmacy aseptic unit
- Characteristics of the microbiological growth media — who provides it, what types are used, whether it is purchased or manufactured by the microbiology laboratory and how its quality is assessed
- The microbiological methods used to culture and identify micro-organisms — how samples are received, stored and labelled and how quickly reports are generated
- Whether provision of specialist microbiological advice is available in the event of unusual or out-of-limits results or following untoward patient events
- Whether extra work or special investigations arising out of, for example, the validation of new equipment, can be accommodated
- Whether the quality and efficacy of the laboratory service is monitored via internal audit or by participation in external accreditation schemes

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