ASEPTIC PREPARATION IN NHS HOSPITALS

INFORMATION FOR MICROBIOLOGISTS

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In the interests of promoting inter-professional understanding and co-operation, this document aims to give relevant background information to hospital microbiologists on the standards that pharmacists are required to implement in the operation of a Pharmacy Aseptic Unit (PAU).

Many hospitals have PAUs, whose function is to prepare sterile medicines. These medicines are usually, but not exclusively, administered by injection. Patients can be harmed by medicines that are incorrectly formulated or non-sterile, and pharmacists are responsible for ensuring that these criteria are met.
Medicines prepared in a PAU may be stored for up to 7 days before administration. As few of these medicines contain antibacterial preservatives, the consequences of low-level contamination, even with non-pathogenic organisms, can be profound.

COMPLIANCE WITH STANDARDS

Following an incident in 1994 when a number of patients were infected by contaminated TPN solutions (some of whom subsequently died), the standards set out in the Rules and Guidance for Pharmaceutical Manufacturers and Distributors (the "Orange Guide"), were formally imposed on the NHS in England by Executive Letters EL(96)95 and EL(97)52. Appropriate monitoring programmes to demonstrate compliance with these standards have been developed by the NHS Quality Control Committee. Implementation of these programmes is also a requirement of EL(97)52.

Although hospital microbiologists may be unfamiliar with these standards, and may not immediately perceive them as appropriate to the hospital setting, pharmacists have developed them in conjunction with the Medicines Control Agency (MCA), and are responsible for their implementation.
MCA Inspectors and Regional Quality Control Pharmacists regularly audit PAUs, and can recommend appropriate remedial action, including closure of a Unit that fails to comply with the required standards and thereby presents a risk to patient safety. The Royal Pharmaceutical Society may, under its Code of Ethics, take disciplinary action against an individual pharmacist who does not comply with them.

STANDARDS FOR WORKING ENVIRONMENTS

The Rules and Guidance for Pharmaceutical Manufacturers and Distributors defines the standards required for the working environment (Table 1). A variety of test methods is required because of the limitations of each in terms of efficiency of recovery of organisms.
An isolator or Laminar Air Flow workstation (LAF) should comply with Grade A.
A room containing a LAF should comply with Grade B (minimum).
A room containing an isolator should comply with Grade D (minimum).
Other adjacent rooms may be of lower classification, but should be monitored, as they may affect the controlled rooms.
Slightly more relaxed standards are applied to PAUs preparing medicines for "immediate use" ie within 24 hours.

Table 1 Standards for working environments

	Limits for microbial contamination			
grade of environment	active air sample cfu/m^3	settle plate cfu/4hours 90mm diam	contact plate * cfu/plate 55mm diam	glove print 5 fingers cfu/glove
A critical zone	<1	<1	<1	<1
B	10	5	5	5
C	100	50	25	no limit
D	200	100	50	no limit

Table 2 Standards for working environments where the product will be used within 24 hours

	limits for microbial contamination			
grade of environment	active air sample cfu/m^3	settle plate cfu/4 hours 90mm diam	contact plate * cfu/plate 55mm diam	finger dabs 5 fingers cfu/glove
isolator critical zone	<1	1 per 2 plates	1 per 2 plates	1
isolator room	500	200	50	not specified

* many PAUs use surface swabs taken from a standard area, typically 10cm x 10cm

MONITORING PROGRAMME

The Quality Assurance of Aseptic Preparation Services (3rd edition 2001) describes the monitoring programme necessary to demonstrate compliance with these standards.

The document sets out to monitor four of the major sources of contamination in aseptic manipulation:

- airborne contamination
- contamination by touch
- surface contamination of components
- contamination during storage

It does not include contamination during administration in this monitoring programme.
Although this paper is primarily concerned with microbiological matters, it should be noted that chemical and physical parameters are also controlled.

The risk of contamination is dependent on a number of key factors, including:

- the environmental standard of the aseptic work zone
- the aseptic technique of the operator
- the use of “open” or “closed” procedures
- the number of additions made

Other risk factors include:

- the anti-bacterial properties, or ability to support microbial growth, of the product itself
- storage times and temperatures
- growth characteristics of micro-organisms
- prolonged infusion times
- container integrity

Data from many sources suggest that the contamination rate for non-automated aseptic manipulations performed in a Grade A environment can be up to 1 in 1000.

MONITORING THE ENVIRONMENT

To ensure that product quality is not compromised, regular monitoring is essential to demonstrate that the controlled work zone complies with the standards.
A PAU should be commissioned before being taken into use, and appropriately re-commissioned following any shut down for maintenance. It is desirable to repeat the commissioning studies at 2-yearly intervals.
A programme of monitoring should be developed for each PAU, based on the recommendations in Table 3.

Table 3 Minimum frequency of monitoring

test	grade A critical zone	other clean areas *
active air sample	three-monthly	three-monthly
settle plate	sessional	weekly
contact plate	weekly	weekly
glove print (finger dab)	sessional	not required

* including isolator transfer hatches

Settle plates are used to provide ongoing validation of environmental control
Glove prints (finger dabs) indicate the likelihood of contamination by touch during the aseptic process. They also give an indication of a failure of sanitisation of ingredients and components during transfer into a controlled work zone.
Active air samples (airborne viable counts) and contact plates or surface swabs give less frequent but more detailed information about environmental contamination which may not be detected by the use of passive settle plates.

TEST LIMITS AND INTERPRETATION OF RESULTS

The limits in Table 1 are Action levels, the levels at which action must be taken. A PAU must have a written Standard Operating Procedure detailing the remedial action to be taken if these levels are exceeded.
In addition, it is helpful to set Warning levels for all monitoring points to give early indication of potential problems.

The interpretation of microbiological data is complicated, due to the imprecision of the various methods used. It requires familiarity with the micro-organisms likely to be present in and around the PAU.
Although individual results may exceed Action or Warning levels, they should not be viewed in isolation. Results accumulated over time are of great value when subjected to trend analysis. Exceeding the warning levels on isolated occasions may not require more action than examination of control systems. However, the frequency of exceeding these levels should be examined, and should be low.
If the frequency is high or shows an upward trend, then action should be taken. At all times the environment must be proven to be under control.

The detection of organisms in controlled areas may indicate a failure of control systems. This may be associated with facilities (e.g. air-handling unit, HEPA filters, room fabric, isolator envelopes, door seals) or practices (e.g. inadequate sanitisation during transfer of components into sterile areas, problems with clean room clothing, poor personal hygiene).
Although identification of each contaminating organism at every site is not necessary, identification does give an indication of their likely source and aids in their eradication. This is particularly useful in critical zones, in cases where Action levels are exceeded, and when adverse trends become apparent.

Helpful classifications include

Gram positive spore forming bacilli, associated with general dust and many packaging materials

water-borne organisms, typically Gram negative motile rods, possibly indicative of contamination from nearby taps & drains, or contamination of cleaning solutions and equipment

yeasts & moulds – seasonal, or associated with building fabric or construction work

skin flora, such as staphylococci, micrococci, diptheroids

gut flora, such as coliforms

More specific identification may be required to address particular problems.

The interpretation of contamination with common environmental organisms as a "false positive" is unhelpful in this context. To minimise the possibility of such results, it is desirable that all media should be pre-sterilised.

MONITORING OF PERSONNEL

All staff working in PAUs must demonstrate their continued competence to perform aseptic work. It is recommended that this should be repeated every 6 months.
This is done by manipulation of sterile culture media, which is subsequently incubated to confirm the maintenance of sterility. A national standard kit is recommended, although others are used.
Finger dab testing, carried out on a sessional basis, forms a specified part of this test, although some units may perform glove or finger swabs.
A local procedure should be agreed for performing this test. It is important that this should be done at the end of a work session, before any equipment or glove cleaning is done.

MONITORING OF PROCEDURES

Aseptic manipulation procedures performed in a PAU should be validated by simulation with sterile media, which is subsequently incubated to confirm the maintenance of sterility.

MONITORING OF PRODUCTS

The microbiological monitoring programme should include sterility testing of finished products. Unused products, or additional samples prepared specifically for testing, may be used. It is not considered safe to sample from products prior to administration to patients.
Sterility testing is required to be performed in facilities that comply with GMP Grade A environmental standards, and follow the methods of the European Pharmacopoeia for sample size, culture media used, and incubation conditions and times.

SPECIAL DEMANDS

A PAU will require extensive microbiology support for specific projects, such as

Commissioning a new or refurbished PAU
Large numbers of sampling points should be monitored daily until satisfactory results are obtained. This will confirm that the facility is operating correctly. If monitoring is begun at an early stage it may identify problem organisms from construction work. It will also demonstrate the effectiveness of the initial decontamination and clean. Results should be used in the selection of the smaller number of sampling points used for ongoing routine monitoring

Validation of transfer procedures
This is to demonstrate that the procedure used for the transfer of materials provides components and materials with surfaces that are free from viable organisms.

Validation of cleaning procedures
Cleaning agents and methods should be similarly validated.

Validation of new processes

Investigation of out-of specification results

MEDIA AND METHODS

The choice of suitable media and culture conditions should reflect the indigenous flora, but most monitoring can be performed using tryptone soya medium. Incubation at 22.5°C and 32.5°C is required. Many laboratories incubate individual samples at both temperatures, e.g. 4 days at 22.5°C followed by 3 days at 32.5°C. The use of blood agar is not appropriate.
To minimise the possibility of contamination and "false positive" results, it is desirable that all media should be pre-sterilised. Non-sterile media should not be taken into critical zones.
All media used for monitoring must be tested and certificated for sterility and fertility before use.

TECHNICAL AGREEMENTS

A formal Technical Agreement is required between a PAU and a Microbiology Service Provider. A model agreement is appended, taken from the Quality Assurance of Aseptic Preparation Services (3rd edition).

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