DESIGN, BUILD AND MAINTENANCE OF PHARMACY ASEPTIC UNITS

EDITION 2

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INTRODUCTION

The chance or need to build or upgrade cleanrooms may come from a variety of sources and at any time (usually when life is at its busiest.) National drivers are:

- Government programme for new hospitals
- Farwell report[1]
- GMP[2]
- NHS Plan[3]
- Spoonful of Sugar[4]
- Medicines and Healthcare products Regulatory Agency (MHRA) inspection reports
- EL(97)52[5] audit reports
- Modernisation of NHS manufacturing units

The reality is that standards change, as do demands for service. Services should be accommodated only by the use of facilities meeting current standards.

Designing and validating, or significantly upgrading, an aseptic suite is a task which many pharmacy staff will be involved with only once in their careers. The majority find the task daunting and often find it difficult to obtain helpful and unbiased advice.

The challenge has become even greater in recent years with the change in emphasis from the Regional level of Planning and Estates function to Trust level, and the increasing reliance on Private Finance Initiatives (PFI). The responsibility on Trust-based pharmacy staff to "get it right" has become enormous.

It was with the philosophy of "let's learn from each other" that this guidance document was conceived. This second edition, now expanded and tailored to aseptic (including isolator) cleanrooms, continues this philosophy. Many excellent texts provide outline standards for pharmacy aseptic facilities[2,6,7]. It is not the intention of this document to replace these standards in any way, but to supplement them with practical advice and indications of pitfalls to be avoided. The topic of design, build and maintenance of cleanrooms can often be very dry, yet it is vitally important for the NHS. The style of this advisory document is deliberately informal so that it is easy to read to encourage staff to refer to it when required to design new cleanrooms.

The following information is meant to give the very broadest guidance on what designers, planners, builders and users may like to consider. It is hoped that it will, by drawing on the experiences of others, play a small part in conserving NHS resources and helping some of its staff.

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1. STANDARDS

1.1 The standards to which new or upgraded buildings and associated equipment must comply should be clear from the outset and unambiguously documented in the user requirement specification (URS), as this is used to develop all room data sheets. Throughout this document the URS is referred to in the singular, however it may comprise of several specifications, eg for rooms, isolators etc. The URS is often required in a relatively short time, but don't be rushed into doing a "quick" job – it is the basis of a successful project.

1.2 It is advisable to quote directly from standards documents wherever possible when setting the URS. The "Premises" section of Annex 1 to EUGMP[2] can be particularly helpful regarding airflows, finishes etc. Health Building Note 14-01[7] is also a key document, as is HTM 03-01[8] (specification for air handling units).

1.3 Current standards need to be knowledgeably interpreted, and future developments considered before the URS is "set in stone". Take advice from suitable sources e.g. Regional Quality Assurance, experienced production and/or aseptic services managers, independent specialists. The importance of fully understanding the processes to be used cannot be overemphasised. Examples of recent URSs can be found on the NHS Pharmaceutical QA Committee Website www.ukqainfozone.nhs.uk.

1.4 The URS should specify key requirements and methods of working, eg gassing technology in detail, however it is advisable at this stage not to be prescriptive about the layout of the unit. The companies tendering may have some good ideas which you hadn't thought of! The HBN 14-01[7] contains some typical layouts which may be helpful, however there only needs to be sufficient information in the URS to allow the selection of a preferred contractor. The expression 'minimum compliance quality' is sometimes used. For example, if you do not state vinyl covering on floors, ceilings and walls some elements may be given a 'biocidal' paint finish or in place of the expensive polished 316 stainless steel you may find powder-coated stainless steel of some lower grade.

1.5 Workflows of people and materials (with an indication of scale of operation and nature of the products) should be provided. Process mapping of the aseptic activities to be carried out in the unit is also advised.

1.6 Ensure that you see the documents (including final URS) that are sent out to tender. Do not assume that all changes discussed in planning meetings have been incorporated. It is advisable to keep your own notes of meetings. There should be version control on all specifications.

1.7 It is unusual for standards to change unexpectedly during the course of construction, as the process of consultation on new standards is lengthy. However it is important to consider any draft proposals that might impinge on the project before completion.

Furthermore, reinterpretation of existing standards (especially by the Medicines and Healthcare products Regulatory Agency (MHRA) inspectors) can occur and could require changes, which are often costly.

1.8 The requirement for the installation of continuous particulate monitoring has been the subject of much discussion with the MHRA. EU GMP requires the installation of continuous monitoring systems in grade A and B areas. It may be appropriate in an NHS aseptic unit not to do so, but in all cases a risk assessment should be performed and documented for each workstation taking into account:

- whether the process is open or closed;
- whether liquid disinfection is carried out or components are Vaporised Hydrogen Peroxide (VHP) sanitised;
- results of particle counting in the occupied state, often indicative of opening packets and using wipes.

Further advice can be obtained from your Regional QA Specialist and MHRA Inspector.

1.9 Closed procedures, including the single withdrawal from an ampoule, have a lower risk of microbial contamination. Spraying of liquid disinfection is likely to cause spurious particle results. VHP sanitisation provides a lower risk environment for aseptic manipulation.

1.10 The risk assessment should also state what routine monitoring is proposed, to prove that the EU GMP classification is maintained, eg session plates, quarterly particulate monitoring etc.

1.11 The unit will probably need to be used for many years in the future. It is important to research the current market, and also plan for future developments in the service eg merging of services from other sites, implementation of NPSA Patient Safety Alert 20[9] (Injectable Medicines).

1.12 It is of critical importance that due attention is given to both capacity and workforce plans when carrying out service development and/or horizon scanning.

1.13 The capacity plan can be written using different available models but must take regard of factors such as patient groups, demographic profiles, treatment pathways, new product developments, changes to standards as well as the usual capacity criteria of quantification and optimisation of cleanrooms, equipment and skill mix (see QA of Aseptic Preparation Services[6], Appendix 5).

1.14 A workforce plan must recognise Government initiatives, Trust service developments and the local recruitment and retention characteristics.

1.15 It is likely that the unit will be built to meet the minimum acceptable standards on initial validation and is unlikely to have spare capacity unless this is included in the URS. The user must consider future needs, as far as can be foreseen, and plan for the maximum standards affordable, with as much flexibility as possible for future developments.

1.16 If the premises are to be licensed, the MHRA GMP Inspectorate may be prepared to comment on plans, but they will not act as consultants. (They are often central in instigating higher standards).

2. SKILLS

2.1 Siting of a new unit may be critical. To avoid cross contamination it should not be adjacent to kitchens, morgues, laundry etc that could introduce microbial contamination. The position of sewers and drains in relation to the unit should be carefully considered. There should be no pipes running across the ceiling of a cleanroom due to the danger of leakage and access to main drains should be well away from any clean areas. Beware of engineers installing "rodding points" within a cleanroom to avoid siting them in patient areas!

2.2 After drawing up a detailed URS, to be sent with the tender documents, it is important to obtain information on potential contractors by talking to other NHS units who have recently completed similar schemes. Would they use the same contractor again? If not, what would they do differently? A visit to the site may be appropriate. Your Regional Quality Assurance Pharmacist should be able to help.

2.3 The project is only likely to be successful if a knowledgeable architect and experienced specialist cleanroom company (including any sub-contractors) are appointed. Before contracts are awarded, their credentials and their experience specifically with pharmacy aseptic cleanrooms (not laboratories or theatres!) should be established, e.g. Do they understand the problems associated with exhaust of isolators? Do they understand how equipment from other companies interfaces with their design? Fire and security systems are often an issue. You do not want your project to be used as their learning experience. It is advisable to interview a selection of potential contractors. It may help with the final decision if previous projects in which they have been involved are discussed. You may wish to contact the customer directly for an independent view.

2.4 Check whether the contractor is intending to sub-contract any (or all!) of the work to other contractors and ascertain their credentials and ability to build cleanrooms. It is advisable to put a note in the tender documentation about not sub-contracting without your approval.

2.5 When selecting a cleanroom contractor it is advisable to obtain examples of qualification documentation with the tender submission including examples of Design Qualification, Installation Qualification etc. If these are not satisfactory consideration should be given to employing an independent validation consultant, especially for PFI schemes.

2.6 For large projects the benefits of taking advice from or appointing a specific validation manager should be considered. This will allow a full current good manufacturing practice (cGMP) review and impact assessment of the project to be undertaken and is often a cost effective step. However, this may not be cost effective if the person appointed does not have specific relevant NHS expertise. In this case local expertise with suitable back-fill may be preferable.

2.7 Workforce planning for the users involved in the project must be considered from the start. It is a lot to ask of staff supplying the current service to take on the management of a new project in addition to their normal workload. They do not have the time to chase up contractors to ensure they comply with the agreed schedule. New MHRA thinking is that lack of resources for quality is a cGMP violation and that senior management is responsible and accountable to assure that quality is properly resourced. Workforce planning during the change to the new facilities is also of critical importance.

3. COST

3.1 The selection of the contractor is normally based on the cheapest quote which fully matches the URS. However, value for money should be the desired aim. It is important to ascertain whether the price has been based on your interpretation of the standards and that the materials to be used are appropriate. There is often a belief at the start of a project that if a contractor has misinterpreted the URS, they will put it right without delay. Experience indicates that this is often not the case (particularly for PFI schemes), hence the importance of a detailed, unambiguous URS.

3.2 The cheapest materials are unlikely to be the best, particularly since the unit must be robust enough to provide a service for a number of years. Consider how the fabric of the building will stand up to use. For example, transfer hatches made from polished 316 stainless steel may be most cost effective.

3.3 All costs such as validation, staffing etc. should be identified. A group within the Trust should meet regularly to review budgets. For example, a validation budget (normally of 5-10% of the project cost) must be established. A realistic equipment budget, including office equipment and general furniture for a new build, must be managed. Funding will also be required for additional staff to support the planning and validation processes. Who controls these budgets should be clearly identified at an early stage.

3.4 Contractors are likely to charge heavily for changes once the project is underway. Be as sure as you can be that the URS is correct, detailed and not liable to misinterpretation.

4 CO-ORDINATION AND COMMUNICATION

4.1 It is important that the URS is prepared as a priority. Delays in the tendering of items of equipment (those over a certain threshold must be advertised in Europe) will result in delays in the decision process on their purchase. This may have implications for air supply, airflow, ducting etc. (which may also have cost implications). Remember there may be a considerable lead time for certain pieces of equipment such as isolators and therefore obtaining a firm commitment to a delivery date is advised.

4.2 It is helpful for an experienced person with good communication skills to act as a co-ordinator between all contractors and clients, particularly when work has been sub-contracted. The appointment of a Project Manager/Engineer may satisfy this requirement. It is essential that all involved in the project work together as a team and have joint ownership of the time schedule. During construction regular site visits and discussions between contractors and users are advantageous. Any subsequent agreed changes should be documented.

4.3 It is also essential that there is good communication between the design stage and hand-over of the unit. Projects often fail if communication is poor, as pharmacy staff and contractors often do not interpret things in the same way e.g. a "smooth finish" has a different meaning to a builder from an aseptic room user.

4.4 Problems are more difficult to resolve (and more expensive) if they are picked up at a late stage. The phrase "turn-key project" often means the user turns the key and is left to sort out the problems!

4.5 Any deficient work, materials or equipment (particularly if supplied by a sub-contractor) may have contractual implications regarding repair, replacement, allocation of blame, or even court proceedings. All of these can substantially hold up the project. If during validation tests fail due to defects it is often difficult and time consuming to resolve. Contractors are reluctant to rectify faults.

4.6 Equipment is classified into four types:

Group 1: items (including engineering terminal outlets) supplied and fixed within the terms of the building contract.

Group 2: items that have space and/or engineering service requirements and are fixed within the terms of the building contract, but supplied under arrangements separate (ie purchased by the Trust usually) from the building contract. (In effect, issued "free" to the contractor).

Group 3: as Group 2, but supplied and fixed (or placed in position) under arrangements separate from the building contract.

Group 4: items supplied under arrangements separate from the building contract, possibly with storage implications but otherwise having no effect on space or engineering service requirements.

It is important that the people responsible for purchase of Groups 2,3, and 4 equipment communicate with the builders to avoid problems eg isolators that won't fit into rooms, or with unsuitable or wrongly positioned services or ductwork.

4.7 The URS for equipment should also be checked carefully, especially for PFIs, as equipment will probably be purchased by a totally separate company from those building the cleanroom. Ensure that they have checked that the specified equipment will actually fit in the rooms, with adequate space for safe operation.

(In one new build two isolators were installed in one room and it was impossible for staff to open one of the hatches due to the adjacent isolator overlapping. The contractor's response to this was "Well they fit in the room, you didn't tell us you needed extra space to use them in!")

5 AIR HANDLING

5.1 A well-designed air handling system is the basis of a satisfactory unit. If this is wrong then the unit is unlikely to ever function satisfactorily. Major concerns are air quality, temperature and humidity control. The EU Grades required for rooms should be clearly specified according to recognised standards.[2,6] Do not be too tight in your specification as it adds disproportionately to the cost. For example, temperature limits of $\pm$1°C are expensive and cannot generally be justified. However no controlled temperature will cause operational difficulties in winter or summer. Consider the staff and the type of garments being worn when setting the temperature control range and allow for heat gain from equipment eg isolators.

5.2 Factors such as the capacity and number of air handling plants (and which specific areas they will serve) are key and must be considered early in the project. The air handling unit (AHU) should be appropriately sized so that it is not required to run at full capacity from the outset. The overall power requirements should also be considered in the design stage. Are service developments e.g. gene therapy likely? If so, separate air handling and extract may be required[6,7,8,10].

5.3 The air handling plant(s) should comply with HTM 03-01[8]. Details such as the requirements for duty and standby fans, number of belts, humidifiers, silencers, inverter drivers etc, should be agreed with the contractor. The position and type of humidifiers within the plant should be carefully considered in line with HTM 03-01[8] in order to prevent saturation of filters. The implications of the fitting of frost coils should be clearly understood. The setting of a frost thermostat may cause the air handling plant to shut down in winter requiring a full clean down of the unit before starting production.

5.4 During the planning stage, serious consideration should be given to the power supply to the AHU. Any interruption to the air supply in excess of perhaps two minutes (found during validation at commissioning) will necessitate a major clean, disruption of work and extra cleaning time, always popular with staff! Interruptions may be scheduled, eg for generator testing, or unscheduled eg for plant or mains failure. The supply to the AHU should therefore be on the hospital emergency power supply.

5.5 It is well worth considering an emergency Uninterrupted Power Supply (UPS) capable of covering power outages. This covers the time before the emergency generators step in, or the time taken for estates/facility management staff to be able to attend plant rooms, investigate the problem and give a reasonable assessment of the situation enabling work within the unit to be continued.

5.6 All sections of ductwork must be supplied in sealed polythene and not opened until immediately prior to installation. The unsealed end of the ductwork should remain protected until the next piece is installed. Blasting the duct clean after installation is not an acceptable alternative.

5.7 The use of flexible ducting should be avoided where possible. If used, care should be taken to avoid wires trailing across it, which may cut into the fabric of the ducting as it moves.

5.8 The siting of the air inlet is vital to the quality of the air and the lifespan of the filter, and should be carefully considered. It should not be sited near to the extract ducts or the car park!

5.9 Air handling plants for pharmacy aseptic units should be dedicated to only these areas and not linked to adjacent areas eg offices, patient waiting rooms. Unless this is the case it is unlikely that DOP testing can be carried out easily, and air balancing will be extremely difficult. The MHRA take a strong line on this.

5.10 Airflow dampers to each leg of the system fitted with a HEPA filter enable adjustments to be made to rebalance the system, for example as filters block.

5.11 If constant volume dampers are used to automatically compensate as filters block, they should be sited where there is access for routine maintenance, without entering cleanrooms.

5.12 DOP access points must be carefully considered at the design stage. The injection point should be sufficient distance upstream from the terminal HEPA filters to allow uniform challenge (at least 15 duct widths from the filters) and must be located outside of clean areas. The position of DOP access points should be marked on the ductwork drawing. Upstream DOP concentration test points will also be required.

5.13 Ideally access to the plant should be controlled by pharmacy with emergency only access by Estates. Instituting a "permit to work" system for maintenance is wise. Estates must report to pharmacy before and after working and record what has been done.

5.14 The contractor may use computer aided technology for airflow modelling predictions at the design stage, particularly for complex rooms. It may well pre-empt airflow problems. Be aware however that not all companies who have this software are able to use it accurately!

5.15 The position of filters and pressure relief flaps is critical to cleanroom design. Often designers like to build units with high-level pressure relief flaps (which take up less room), and high level extract (which conserves heat). This philosophy is contrary to MHRA opinion which is for high level input and low level extract, as flushing of the room is generally inefficient

with high level air entry and exit. Annex 1 to the EU GMP Guide[2] can be usefully quoted in cases of dispute.

5.16 Alternatively it is possible to design cleanrooms with individual supply and extract to each room. Extract grilles should be at low level. (In this case it may be acceptable to have a small pressure relief flap above a door to maintain the pressure differential in addition to low level extract.) Room extracts should be carefully designed to avoid any uncleanable exposed ductwork.

5.17 Beware of designs which have grilles in cleanroom doors as engineers may put packing behind the grille when balancing. The packing can move as the door is used, which disturbs the pressure cascade. The movement of the door could also alter settings of grilles/dampers.

5.18 Equipment must be 'designed into the rooms'. For example, extract from an isolator or airflow from a horizontal laminar flow cabinet should be taken into account when designing the airflow patterns in the room in which they're housed. Wherever possible future developments, eg a second isolator or laminar flow cabinet (to be purchased at a later stage) should be considered. Heat gain and noise from a second workstation may also be problematic.

5.19 With extract isolators or Class II safety cabinets, consideration should be given to the consequences of switching off the extract for maintenance. Contractors sometimes propose "thimble" systems to prevent pressure increasing when an extract cabinet or isolator is switched off. In these circumstances you need to be sure that the airflow pattern will not be compromised. Alternatively contractors may use pressure relief flaps to prevent over-pressure in the room when the extract is switched off. In these circumstances the position of the pressure relief flaps are less significant than for normal operation.

5.20 The correct type of diffuser should be fitted to each HEPA housing. For example, swirl diffusers are particularly good at distributing air in the clean end of a change room. However, a 4-way diffuser will distribute air predominantly across a ceiling. In all cases the diffusers should not be sealed, to allow them to be removed for testing or replacement of HEPAs.

5.21 Airflow patterns should be checked at hand-over stage to ensure that they achieve any predictions, in practice. Particular care should be taken to look for dead spots, eddies, and around pass through hatches in a combination of open and closed doors.

5.22 All rooms and corridor areas in a cleanroom suite that are classified must be fitted with terminal HEPA-filtered air supplies. For change and support areas, the majority of the specified room air changes must come from filtered supply rather than bleed air.

6 FABRIC AND DESIGN

General

6.1 Once the preferred contractor has been selected it is important to finalise drawings and obtain detailed room data sheets plus pictures of fixtures and fittings. It is a good idea to sign these off and keep them in a safe place to produce if you do not think you have been given what was specified. Pressure relief flaps can mysteriously move or doors hang the wrong way round!

6.2 The principles of EU GMP[2], e.g. easily cleaned smooth finishes, absence of exposed wood throughout the unit etc, should be stressed at an early stage, and continually monitored during the project.

6.3 In all cases specific details of the actual items to be installed should be provided by the contractor, e.g. doors, benches.

6.4 A 'mock-up' of the cleanroom showing finishes, coving, light fitting, hatches etc can be helpful at avoiding snags , and should be seriously considered, particularly for large schemes.

6.5 Coving around floors, walls, and ceilings often causes particular practical problems. A commonly used radius of curvature for coving is 40mm (38mm cove former) for an internal corner, and 15mm radius for an external corner. Curvatures must be compatible at all joints e.g. where walls meet floors or ceilings.

NB. Coving must be applied before any final wall finish, e.g. vinyl. Vinyl coving must be adequately supported (no gaps in the former) and cladding must be adequately bonded.

6.6 Windows should be effectively and permanently sealed and the seal checked with smoke. Window sills, hinges, handles and locks are not required! If present, gaps between cleanroom windows and external windows should be adequately sealed to prevent ingress of dust, insects, condensation etc.

6.7 All connections to uncontrolled environments must be adequately sealed eg electric sockets, smoke detector, intercoms. Special cleanroom products should be used wherever available.

6.8 All joints should be flat and smooth. Joints between vinyl sheets need to be sealed by welding then made flat and smooth. Joints between panels also need to be flat and smooth using appropriate silicone sealant. (Ask to see an example or a 'mock up' to check the standard of workmanship.)

6.9 Vision panels, switches, lights, sockets etc should be flush fitting and easily cleanable. Use of stainless steel is more expensive but more durable, although care must be taken to avoid any prolonged contact with chlorine based disinfectants to prevent pitting of the surface.

6.10 However, beware of men bearing guns of silicone sealant to solve any problem – they are not an alternative to good workmanship!

6.11 Walls and ceilings must be able to maintain working pressures within normal tolerances, including change and support areas. For example, perforated ceiling tiles are unacceptable.

6.12 Ducting should have individual dampers to allow filter change and maintenance without affecting the integrity of the remainder of the system.

6.13 The use of access doors, access hatches or the removal of light fillings to get to the space above the cleanroom should be avoided to prevent loss of integrity.

6.14 Filters are easily damaged and should be fitted at a late stage, then protected. An alternative is to use "sacrificial" filters and replace them just before handover.

6.15 Filter housings are also critical components of the unit and should be treated with equal care. They can be distorted if transported or handled without due care. Subsequently filters will then never seat and seal correctly.

6.16 Standard size filters should be used whenever possible, as there will be problems with reliable supply of replacement HEPAs where non-standard sizes are used.

6.17 Fire exits require careful planning. Fire officers can often insist on features totally inappropriate to cleanrooms e.g. standard push bar fire escape doors from Grade B rooms. Consult them early to resolve any problems in the plan. Removable panels are preferable to traditional fire exit doors. Escape routes do not always have to be located in the final room and the support room may be acceptable. Heat and/or smoke detectors may be utilised in supply and extract ducting to prevent the need for uncleanable devices in cleanrooms. Any detectors/sounders in the controlled area should be semi-flush (partially sunk) fitting. Zoning for smoke detectors should also be carefully considered and easily isolated as a block during DOP testing (see 8.5).

6.18 Sinks should be avoided inside all aseptic suites, although there must be provision for hand-washing prior to entry. In certain circumstances, eg radiopharmacy a designated disposal sink is a Health & Safety requirement, but should be sited in the support room well away from the transfer hatch.

Doors

6.19 Doors are a particular problem area. The way they open should be carefully considered, with overhead door closers (if essential) on the "dirty" side.
NB If fitted on the wrong side, the surface of the door will be permanently damaged when the error is corrected.

6.20 In Grade B rooms integrated door closers and hinges (known as spring hinges, with adjustable tension) are often supplied and are preferable to overhead door closers. Concealed hinges are the best option as they don't act as dirt traps.

6.21 An interlock or warning system should ensure that both changing room doors cannot open simultaneously. Emergency door release switches must be present in the rooms where personnel may get trapped, not on the walls in adjacent areas! They must fail-safe (open in the event of power failure) and be demonstrated to work.

6.22 Doors of changing rooms must open so as not to expose members of staff in the process of changing. ('Do not enter' lights should be conspicuous). Vision panels in doors of rooms used for full change are not politically correct, and will be obscured unofficially!

6.23 If vision panels are appropriate, they must be flush with the door on both sides.

6.24 Handles must be designed specifically for cleanrooms. Push plates should allow doors to open without the need for touching. Double swing can cause problems maintaining pressure differentials so doors should open into the room for this reason.

6.25 A lock on the aseptic suite entry door (from the uncontrolled area) opened by a catch from the inside, can prevent unauthorised entry by the curious in the out of hours situation. An emergency key must be available though.

Hatches

6.26 Hatches should be of appropriate size and material considering the nature and extent of the workload of the unit. Handles and hinges should be robust. Separate in and out hatches aid workflow and are preferable to a single hatch with a shelf. Standard size hatches (600mm x 600mm x 600mm) are normally cost effective and more readily available, but may not be suitable in all cases.

6.27 Hatches must be flush fitting on the cleaner side. Corners must be coved and joints made smooth.

6.28 Stainless steel will be more durable than melamine, but will be more costly. If used, the grade (normally 316) should be stated.

6.29 Doors made from glass provide vision and should allow some leakage of air, which should be taken into account in designing the air supply rate. They shouldn't annoy staff by whistling though! Hatches with their own terminal HEPA-filtered air supply and extract may be used when appropriate.

6.30 Hatches must have at least two doors and must be interlocked to prevent them being opened simultaneously. Interlocks should be reliable and correctly set to prevent damage to the doors themselves.

Step-over Benches

6.30 These should preferably be of free-standing stainless steel construction to allow for cleaning. They shouldn't be a barrier to flow of air from the clean to the dirty side.

Controls

6.31 Pressures in all cleanrooms must be monitored using manometers or magnehelic gauges. It is important to specify the location of the pressure sensors in order to determine which pressures are being monitored. Normally steps of 10Pa are used to build a pressure cascade with a minimum differential of 15Pa between classified and unclassified[2] areas.

6.32 Differentials between rooms must be monitored and, if absolute pressures (with reference point) are measured, staff must calculate differentials. Direct measurement of differential pressure is therefore less prone to error. Incline manometers should be avoided as they require regular maintenance and even the relative density of filling fluid must be controlled. Pressure differentials across terminal HEPA filters must be monitored in addition to room differentials. Generally HEPA filters require replacement when the pressure differential across them exceeds 500Pa. Consideration should be given to replacing all HEPA filters supplied by the same air handling unit to maintain the balance of the unit.

6.33 Pharmacy staff must be able to ascertain if there have been any out of hours air supply problems. It is important not to rely on a Building Management System (BMS) system for this information. A pressure sensor in the supply duct connected via a relay switch to a visible alarm that requires a controlled reset and is not automatically reset is often used. The system should be failsafe if a bulb blows. An example could be either a light going on and a light going out, or simply a light going out. The indicator board must be at the entrance to the cleanroom suite and only appropriate staff should be able to reset the alarm. An audible alarm provides additional security and should be installed. Any alarms should be included in the planned preventative maintenance programme.

6.34 Any other alarms, differential pressures, fire indicators or power controls, eg light switches for non-critical services should also be readily accessible at the entrance to the suite.

7 VALIDATION, CLEANING AND HANDOVER

Validation and Qualification

7.1 Validation, often termed "commissioning" for a new unit, should be at three levels

- As built
- Unoccupied
- Occupied

The composition of the validation team is vital. Establish at an early stage who will be responsible for the different levels of validation, e.g. Installation Qualification (IQ) (see 5.5, 5.6) and what experience they have. Contractors carrying out validation should be familiar with the equipment they are using and knowledgeable in the interpretation of results obtained. They should also be familiar with the appropriate standards for testing, e.g. ISO14644[11], EU Guide[2] etc. Check that calibration test certificates for equipment being used are in date and ask for copies for the validation master file. It is not unknown for validation engineers to claim the HEPA filters have passed their integrity test whilst apologising for the whistling noise due to the leak around the filter housing. Occasionally visible holes have been seen immediately after satisfactory DOP test documentation has been presented for acceptance!

7.2 Establish what documentation validation engineers will produce for the process, and whether this is acceptable e.g. are grades of rooms stated in the way in which you are familiar? It is usual to accept a contractor's report only if the tests have been observed by an appropriately trained member of pharmacy staff.

7.3 All three stages should be thoroughly documented in a comprehensive Validation Master Plan (VMP)[2,12]. Realistic timescales should be allocated to the various elements in the VMP, e.g. equipment validation. It is essential that this is comprehensive and will be able to be interpreted and explained to an auditor, e.g. MHRA inspector at a later date. Results obtained by validation engineers should correlate with those obtained independently by pharmacy quality control staff, or any discrepancies able to be accounted for, e.g. alternative methodology. The users must be aware of all aspects of the functioning of the unit, and confident that all aspects of the validation are complete before acceptance. Advice from external sources, e.g. MHRA, Regional Quality Assurance may be helpful.

7.4 The terms 'validation' and 'qualification' are often confused. Validation is the overall action of proving, in accordance with the principles of GMP, that any procedure, process, equipment, material, activity or system actually leads to the expected results. Qualification is the action of proving that any equipment works correctly and leads to the expected results i.e. testing. The relationship between validation and qualification is similar to that between quality assurance and quality control i.e. the former term is of much wider scope than the latter.

7.5 Qualification can be conveniently broken down into the stages of:

- Design Qualification (DQ)
- Installation Qualification (IQ)
- Operational Qualification (OQ)
- Performance Qualification (PQ)

"Snagging" (minor defects, e.g. poor finish) should not be confused with IQ. It should, however, be thoroughly documented.

7.6 Using the analogy of a car, if you wanted a 2 litre car, for example, design qualification would test that you had the correct specification, and IQ would test that a 2 litre engine had been installed in it (not, for instance, a 3 litre one). OQ would check that the engine worked and PQ that it was giving the correct power output.

7.7 It may be a requirement for large pieces of equipment e.g. isolators, that factory acceptance tests (FATs) and site acceptance tests (SATs) are performed by the supplier. In this case these should be carried out between the stages of DQ and IQ.

7.8 Users should witness these tests and ensure that associated documentation produced by the supplier is comprehensive and easily interpreted at a later date.

Cleaning

7.9 A cleaning schedule should be established as part of qualification. For Grade B cleanrooms it often isn't possible to demonstrate compliance with EU GMP standards[2] before a full pharmaceutical clean – however the cleaning process can't be subsequently validated. Normally contact plates and/or swabs are used after the "builders' clean" to determine initial bioburden and microbiological flora. There is then a sequence of cleaning agents and monitoring to demonstrate reduction of contamination to acceptable levels, i.e. validate the cleaning regime. (See NHS QA Advisory document "Cleaning of Aseptic Facilities[13]".)

7.10 Cleaning schedules may require modification in the light of test results, for example, the frequency may need to be increased or the type of agent changed.

7.11 In addition to the general advice given on cleaning in the Quality Assurance of Aseptic Preparation Services standards[6], there are special considerations for a new facility. Compatibility of surface finishes with cleaning agents should have been established at the design stage, but should be closely monitored when routine cleaning schedules are instigated.

7.12 Wall and floor treatments may have been applied at the construction stage, and may be removed over time by particular cleaning agents. Re-application, or use of alternative cleaning methods, may be required.

Handover

7.13 A new facility should only be accepted after completion of a thorough and independent validation programme which proves that the premises, at rest and in the occupied states, are satisfactory both physically and microbiologically for the processes to be undertaken.

7.14 Do not be stampeded into moving into unsatisfactory accommodation to enable the contractor to meet their deadlines. Your 'backstop' facility could be removed and you will be deemed to have accepted your new premises.

Other Aspects of Validation

7.15 After handover, process validation must be carried out to allow the actual preparation of products. This may include review of documentation, preparation of test products etc. In the car analogy, used earlier in relation to qualification, this is equivalent to a road test.

8 MAINTENANCE

8.1 It is essential that, after satisfactory validation, premises are regularly inspected for physical defects and carefully monitored for any other problems eg with the air handling system. This should be incorporated into the internal audit schedule, but there is merit in more frequent inspections in new premises due to possible settlement. A detailed 'twelve month snagging' check should always be included, nonetheless.

8.2 All problems, and their subsequent resolution, should be adequately documented and the records retained for future inspection.

8.3 In today's climate of private finance initiatives, it is possible that the company responsible for maintenance may have had no involvement with the project until hand-over. They will consequently have no awareness of problems encountered during validation. They may also have limited knowledge of the design of plant and equipment and the actual function of the unit that it is supplying. The pharmacy staff involved during validation may be the key to continuity of information and standards. To this end it is important to include in the handover documentation a copy of the relevant drawings and information relating to system design, controls, air handling plant, rooms, fixtures and equipment, together with validation results and planned preventative maintenance schedules.

8.4 It is possible too that the building may not belong to the Trust and may be maintained by a private company. In this scenario it is important to establish where the responsibility for maintenance, monitoring, and terminal HEPA replacement and testing lies (the landlord, the service provider or the pharmacy? – or agents for any of them!)

9 SHUTDOWNS

9.1 These can be of two types

- Planned
- Unplanned

Planned Shutdowns

9.2 Fire alarm testing is carried out regularly (usually weekly) in hospitals. It is important to make sure that your ventilation plant does not shut down in response to these tests, or to fire alarms in other parts of the hospital. If this is the case, the service will be disrupted and the aseptic suite will be out of specification if the fire dampers do not reset correctly and return to their original validation positions.

9.3 Generator tests may also result in shutdown and a time delay before the ventilation system comes up to speed again with the emergency supply. When the main power is restored there will also be a short interruption. It is important that there is a time lag built into the system if there is active extract so that extract is not restored until supply has been established. This prevents the aseptic suite running at negative pressure, compromising its integrity, which may not be rectified by "flushing".

9.4 Planned shutdowns may also be required for other reasons eg refurbishment of facilities, equipment repairs or servicing etc. In this case it is sensible to use the 'down time' to maximum benefit and incorporate as many maintenance procedures as practical.

9.5 Planned shutdowns should be carefully considered in terms of subsequent cleaning and time allowed for "flushing" before normal use is resumed. Appendix 1 gives some suggested measures.

Unplanned Shutdowns

9.6 These can result from structural, mechanical, electrical and software problems. Their cause may not be obvious. It is important to ensure that there is sufficient information available at hand-over to allow appropriate investigation of problems in the future.

9.7 Unplanned shutdowns may be due to genuine emergencies e.g. actual fire, power interruption. They may also result from contractors "messing about" with the plant. The importance of a well-controlled "permit to work" system cannot be stressed enough.

9.8 All shutdowns, no matter what their cause, should be thoroughly investigated at a senior level, clearly documented and corrective action appropriately explained.

9.9 No changes should take place to any validated system unless a change control system is followed. Change control is a formal system by which qualified staff with appropriate backgrounds review proposed or actual changes that might affect the validated status of facilities, systems, equipment or processes. The intention is to decide what action is needed to ensure that the system is maintained in a validated state. The assessment of likely impact on product quality must be carefully carried out and conscientiously documented including risk analysis **before** authority is given for the change.

10 MONITORING

10.1 Installation of sophisticated building management systems (BMS), in the opinion of many designers, negates the need to have real time measurements e.g. differential pressures. The MHRA have expressed the view that if a BMS is to be relied upon, it should be a dedicated pharmacy cleanroom system which they would expect to be validated to GAMP 5[14]. If a hospital-wide BMS system is to be relied upon, in this inspector's opinion, revalidation would be required after any change anywhere in the system! This view effectively makes an independent monitoring system essential for pharmacy cleanrooms.

10.2 "Real time" alarms, with the ability to interrogate the central system remotely for detail, may be a suitable compromise if adequate safeguards can be built into the system and appropriately validated.

10.3 The calibration of any automated monitoring systems is crucial, eg pressure measurement, and must be traceable to recognised standards.

10.4 A programme should be established for routine environmental monitoring following handover[6].

10.5 The use of DOP will trigger smoke detectors unless affected areas are isolated. (The ability to isolate all areas likely to be affected e.g. with common ductwork, should be carefully considered at the design stage.)

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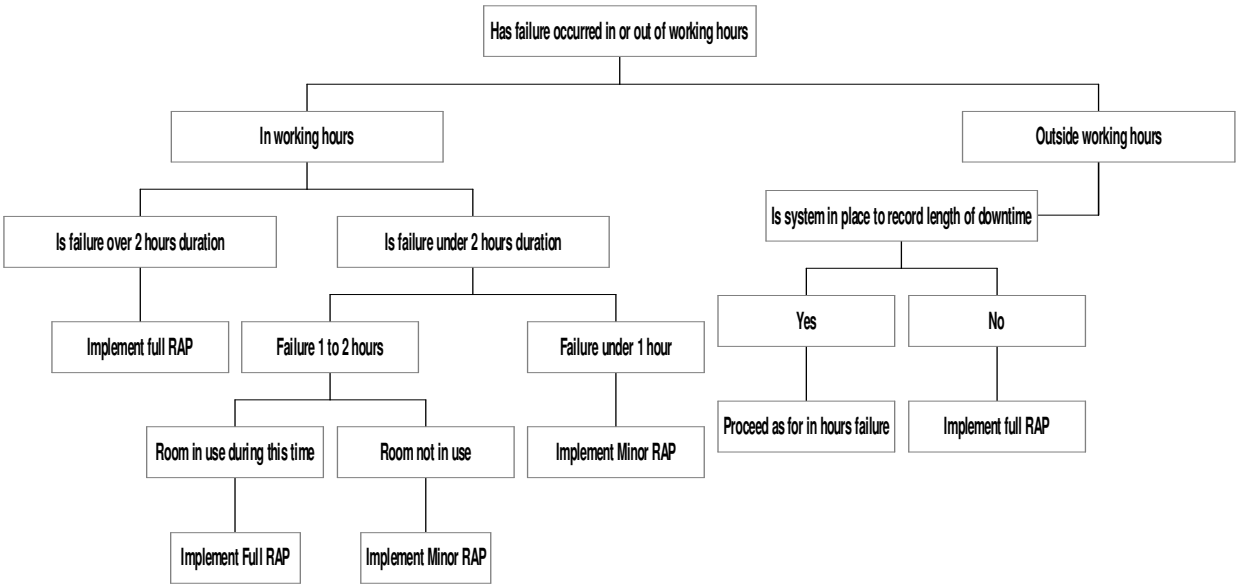
Appendix 1

DECISION TREE FOR ACTIONS TO BE TAKEN IN EVENT OF AHU FAILURE.



Minor Remedial Action Plan.

- 1. Documentation
- 2. Extra microbiological environmental monitoring (settle plates) on day of shutdown.
- 3. Surface Clean
- 4. Extra cabinet/isolator clean
- 5. Minimum expiry time (maximum 24hrs) on day of downtime
- 6. Confirm pressure differentials returned to pre shutdown levels.
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Full Remedial Action Plan

1. 1. Documentation
- 2. Extra microbiological environmental monitoring (settle plates, active air sampling and swab/contact plates) until satisfactory monitoring results obtained.
- 3. Particle counts (after cleanup period) until satisfactory monitoring results obtained.
- 4. Full clean of unit to be done daily until satisfactory monitoring results obtained.
- 5. Extra cabinet/isolator clean to be done daily until satisfactory monitoring results obtained.
- 6. Minimum expiry (maximum 24hrs) until satisfactory monitoring results obtained.
- 7. Confirm pressure differentials returned to pre shutdown levels.